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SURGERY

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SURGERY

VOL. 28 JULY, 1950 No. 1

Original Communications

RESISTANCE OF EXPLANTED GASTRIC MUCOSA TO VARIOUS CHEMICAL AND PHYSICAL AGENTS

JOHN REGIS MILLER, M.D.,*† J. F. HERRICK, PH.D.,† FRANK C. MANN, M.D.,† JOHN H. GRINDLAY, M.D.,† AND JAMES T. PRIESTLEY, M.D.,‡ ROCHESTER, MINN.

INTRODUCTION

THIS study was undertaken to determine the possibility of destroying the function of the parietal cells of the stomach, namely, the secretion of hydrochloric acid, by means of some chemical or physical agent. Such a study, it was realized from the beginning, would involve the use of a number of chemical and physical agents, a determination of the amount of damage done to the secreting cells of the stomach by these agents, and a follow-up study of the regeneration of the gastric glands.

Serious consideration was given to the selection of a suitable preparation to be used in this study. Since Beaumont[1] published his classic observations in 1833, many methods have been devised to study the gastric mucosa and its secretions. It was felt that this study would be greatly facilitated and better controlled if it were possible to transplant a portion of the fundus of a dog's stomach, with its blood supply intact, to the anterior abdominal wall, and have this explanted mucosa secrete hydrochloric acid in response to food or chemical stimulation. By such a procedure, gross observations could be made and, when indicated, tissue for biopsy could be taken and microscopic sections studied. The presence or absence of hydrochloric acid on the explanted mucosa was used to judge the effect of these various chemical and physical agents on the function of parietal cells.

REVIEW OF THE LITERATURE

Various investigators have made claims that a great many chemical and physical agents would prevent the secretion of hydrochloric acid. Few investigators stated definitely whether the decrease in acidity was either transitory or permanent. The following brief review of the literature is limited to those investigations in which the agent used gave promise of decreasing gastric secretion.

Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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*Fellow in Surgery, Division of Experimental Medicine, Mayo Foundation.
†Division of Experimental Medicine, Mayo Foundation.
‡Division of Surgery, Mayo Clinic.

Luck and Seth[2] found that the enzyme "urease" occurs in the gastric mucosa of the Carnivora. Rigoni[3] reported that he found evidence of urease in the wall of the human stomach. Quastel[4] showed that quinone was inhibitory to urease. Mann and Mann,[5] in an experimental study of some chemical inhibitors of gastric acidity, found that quinone in 0.01 per cent solution caused a transitory achlorhydria in dogs.

Necheles and Meyer[6] observed that oil of peppermint applied locally to secreting gastric mucosa caused a suppression in the free flow of hydrochloric acid which is not associated with a relative increase in buffer activity. They concluded that the mechanism was in all probability a local one.

Dodds and Noble[7] reported that the posterior lobe of the pituitary was found to contain a substance capable of inducing a severe lesion of the acid-bearing area of the stomach. These investigators found that the extract was active by mouth and concluded that the substance has a direct toxic action on the cells of the acid-secreting area of the stomach, or perhaps that it stimulates secretion of hydrochloric acid to a damaging extent. Culmer, Atkinson, and Ivy[8] concluded that the anterior pituitary-like fraction of human pregnancy urine contains a substance which depresses the gastric secretory response of a dog to a meal. Nasio[9] found that the prevention of cinchophen ulcer with intramuscular injections of stilbestrol was the result of its epitheliotropic and vasodilating action, particularly by its indirect effect of depression of peptic activity, which is of main importance in the genesis of experimental and human ulcer.

Wolf and Wolff[10] noted that drugs in common use produced no effects on the human stomach and that to noxious chemical stimuli the gastric mucosa is extraordinarily resistant. In fact, it is better protected than the skin itself.

Michon and Magrou[11] reported on the spontaneous regeneration of gastric mucosa after partial gastric resection and found that the muscularis mucosae failed to regenerate. Four years later Ferguson,[12] in a cytologic study of regeneration of gastric glands following experimental removal of large areas of mucosa, found that regeneration of gastric mucosa does occur and described the mucosa as slightly roughened, without rugae, and pinkish in color.

Meyer, Cohen, and Carlson[13] showed that external heat, when sufficient to induce temperature elevations of 2° to 4° F., causes the same changes in gastric juice as produced by fever. These investigators found that the most striking feature was a depression of gland cells, and that the cell changes are transitory in character and probably in the nature of cloudy swelling. They induced fever as high as 105.9° F. in their experiments on animals.

Leden, Herrick, Wakim, and Krusen[14] reported their experimental results on the use of microwaves and discussed the application of microwaves in heating living tissues. Palmer[15] published his work on the effect of short-wave diathermy on the secretory activity of the fasting normal stomach and concluded that short-wave treatment has no demonstrable effect on the values for free or total acid of the normal fasting stomach.

Harvey and Loomis[16] observed the action of ultrasonic waves under the microscope, and found that, owing to the generation of strong eddies by these

ultrasonic waves, cells, at first round, were distorted and stretched, losing their color in the process, and were finally broken up and dispersed into a number of small particles. The great differences of pressure resulting from cavitation caused the cell membranes and smaller microorganisms to be torn to pieces.

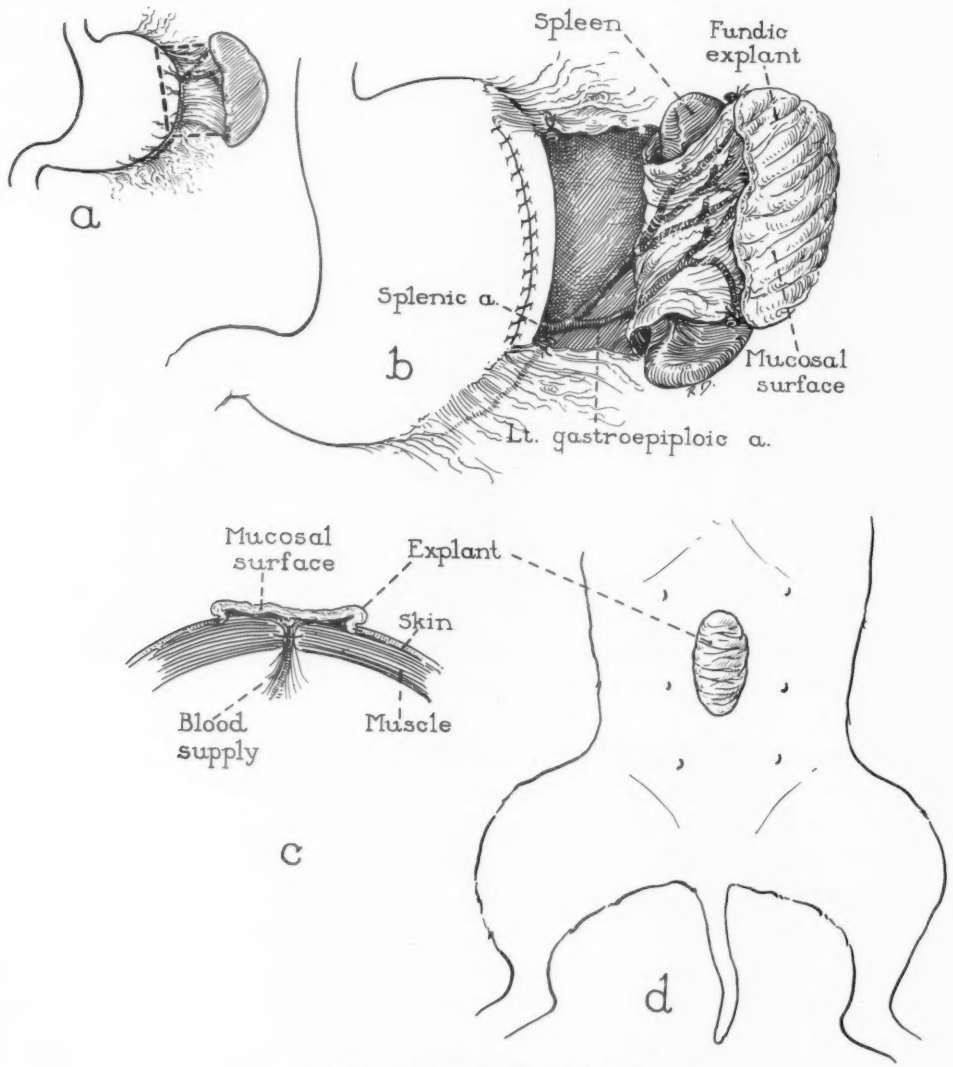

Fig. 1.—Method of explanting gastric mucosa.

MATERIALS AND METHODS

Dogs were used exclusively in this study. With the dog under ether anesthesia, and with sterile technique, a portion of the fundus comparable to that portion used by the physiologist in preparing a Heidenhain pouch was brought out through a laparotomy incision along with its intact blood supply (Fig. 1). The mucosa was loosely sutured around its circumference to the edge of the skin after an elliptical-shaped portion of skin, corresponding roughly in size and shape to that of the explant, had been removed. Healing around the explanted mucosa readily took place and in most instances the dog was ready for

observations within fourteen days. The dogs were entirely comfortable with these explants and the experiments that were carried out caused them no detectable discomfort. One milligram of histamine base was injected subcutaneously to stimulate secretion of acid. The presence or absence of acid on the explant was determined by Guenzburg's test[17] or by applying universal indicator paper directly to the explanted mucosa and comparing the color change with the standard color for various hydrogen ion concentrations. It is realized that the methods of ascertaining the presence or absence of hydrochloric acid may be inadequate to measure all changes. However, carefully repeated observations were made in order to minimize this source of error. The various chemical agents were applied directly to the explanted mucosa by means of gauze sponges saturated with solutions of the chemicals under investigation.

When there was any question as to the efficacy of the solution under various conditions, for example, in the presence of acid, applications were made when the mucosa was in a resting state in which no acid could be demonstrated, and in a state of activity when acid could be demonstrated at the time of application. In most instances the chemicals were applied on three successive days. The average length of time the substance was in contact with the mucosa was one-half hour. Acid was demonstrated on the explanted areas on several occasions before any experiments were undertaken. Immediately after the exposure, histamine was injected and the tests for the presence or absence of hydrochloric acid on the exposed area were carried out.

Hyperpyrexia was induced by the rebreathing of warm vapor in a box enclosing the dog's head, advantage being taken of the fact that a dog throws off excess body heat through his respiratory mechanism.[18] After a control reading was established, rectal temperatures were recorded at five-minute intervals. Histamine was injected subcutaneously twenty minutes before the estimated time of maximal temperature, so that the secretory activity would be greatest at the time of highest rectal temperature. Gross observations as to the appearance and secretory activity of the mucosa were noted, together with determinations as to the presence or absence of hydrochloric acid.

A portable model of a microwave generator producing continuous microwave energy at a frequency of 2,450 megacycles per second, corresponding to a wave length of approximately 12 cm. was used to observe the effect of these microwaves on gastric mucosa. Four dogs were used in this study. The directors were placed 1 inch (2.5 cm.) from the explant and various outputs ranging from 37.5 to approximately 125 watts were tried. To measure the local temperature of tissues, the technique which has been approved by the Council on Physical Medicine for the study of the effect of diathermy was employed; namely, the use of thermocouples before and after exposure to high-frequency waves. Needle thermocouples were inserted into the submucosa, and surface temperatures were taken with contact thermocouples. Photographic records of control temperatures were made, the microwaves were applied, and temperatures were taken immediately after exposure and until the control level was reached.

The effect of ultraviolet irradiation on the explanted mucosa was determined by using an air-cooled mercury quartz vapor arc lamp. The mucosa was exposed for 6 minutes at a distance of 24 inches (about 60 cm.), which, for the particular lamp used, was equivalent to nine times the calculated minimal erythemal dose. On the second and third days exposures equivalent, respectively, to eighteen and seventy-two times the minimal erythemal dose were carried out.

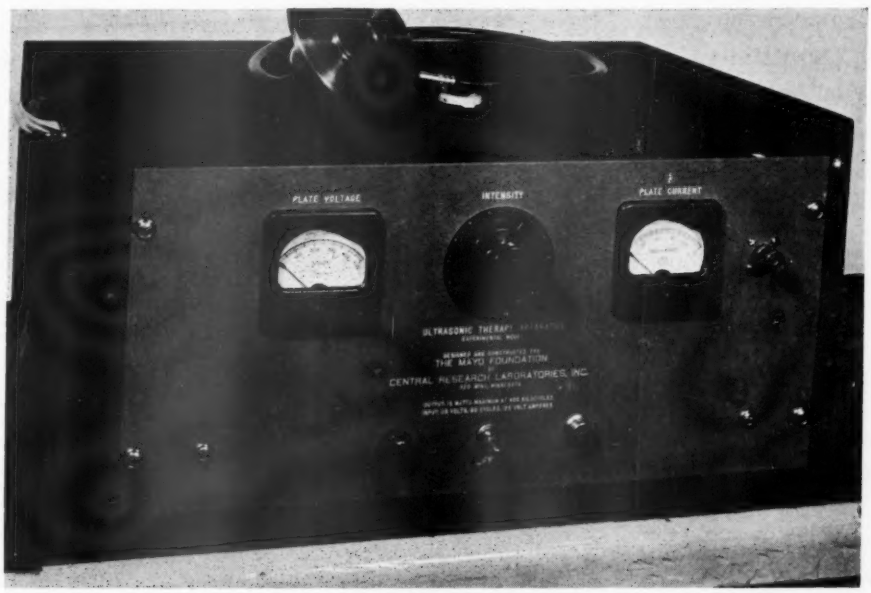

Fig. 2.—Ultrasonic generator and head.

Fig. 3.—Method of application of ultrasonic waves to explanted mucosa.

Ultrasonic waves having a frequency of 800,000 cycles per second from a generator with a maximal output of 15 watts were applied to the explanted gastric mucosa for three one-hour periods on fourteen consecutive days (Figs.

2 and 3). The apparatus was designed from the basic principles employed by the German investigators, and consists of a small, portable generator with a flexible lead attached to the sound head. This sound head contains a quartz crystal mounted behind a small diaphragm. The quartz crystal, which vibrates with a natural frequency of 800,000 cycles per second, is partially surrounded by oil. The explanted mucosa was enclosed by a Lucite cylinder. The cylinder was filled with boiled water and the sound head was placed over it in such a manner as to exclude all air, since it has been demonstrated that the presence of air disperses the effect of the ultrasonic waves.

No quantitative estimations were undertaken owing to difficulty of accurately collecting the secretions from the explanted mucosa.

RESULTS

Repeated applications of 5 and 10 per cent solutions of tannic acid and sodium morrhuate produced no gross changes in the mucosa, nor did they interfere with the function of the parietal cells, that is, with the secretion of hydrochloric acid.

A 50 per cent solution of zinc chloride applied to the mucosa produced a grayish-white membrane over the mucosa, and microscopic sections showed areas of hemorrhagic destruction of the mucosa and submucosa. However, certain areas of this mucosa showed definite secretion of hydrochloric acid in response to stimulation with histamine. When a saturated solution of zinc chloride was applied to the explant, a grayish-white necrotic slough formed, extensive hemorrhagic destruction with complete disruption of the glands was seen microscopically, and no acid could be demonstrated after stimulation with histamine.

Gradual healing of this mucosa over a one-year period was observed. Grossly, the explant gradually regained its normal pink color, but no rugae have been seen to date. After three months a small area in the lower one-third of the mucosa was found to secrete hydrochloric acid in response to stimulation with histamine. Month by month this acid-secreting area increased in size, and after one year there was a demonstrable secretion of acid over almost the entire lower third of the explant. Microscopically, this area showed healing and regeneration of gastric glands.

Oil of peppermint was applied to the explanted gastric mucosa by means of gauze sponges, which were allowed to remain in contact with the mucosa for periods of one-half hour on three successive days. Para-aminobenzoic acid, Hykinone and protamine solutions were also applied in similar fashion. Following these exposures there were no gross or microscopic changes in the mucosa, and histamine stimulated the secretion of acid on the treated area.

Quinone in a saturated aqueous solution was applied to the explanted gastric mucosa. After fifteen minutes the dog vomited, indicating toxic absorption from the explant, but no gross changes were noted in the mucosa, and following stimulation with histamine the mucosa secreted hydrochloric acid.

Anterior pituitary extract, Pitressin and Pitocin were applied to the explanted mucosa. Pitressin temporarily changed the gross appearance of the

mucosa to a grayish-white color for a period of a few hours, but none of these pituitary extracts prevented the subsequent secretion of hydrochloric acid.

Hyperpyrexia was induced in three dogs. Rectal temperatures of 108° F. were induced. The hyperthermia had no immediate or delayed effect on the secretion of acid and did not change the appearance of the mucosa except for a noticeable dryness and diminished secretion at the height of the temperature.

The effect of local heat produced by microwaves on the explanted mucosa was studied. Because of the rich blood supply and the presence of mucus it was impossible to increase the temperature of the explant more than 2° or 3° C. However, when Pitressin was injected intravenously there was a marked blanching of the mucosa lasting for five minutes. Microwaves applied during this period produced temperatures as high as 49° C. (120.2° F.) (Fig. 4). Two areas of blister formation were observed on the explanted mucosa of one dog as a result of this heating. These areas underwent necrotic changes, healed in fourteen days, and the entire mucosal explant continued to secrete acid. Aside from the temporary injury due to the procedure, the mucosa showed a marked functional and structural resistance to the microwaves.

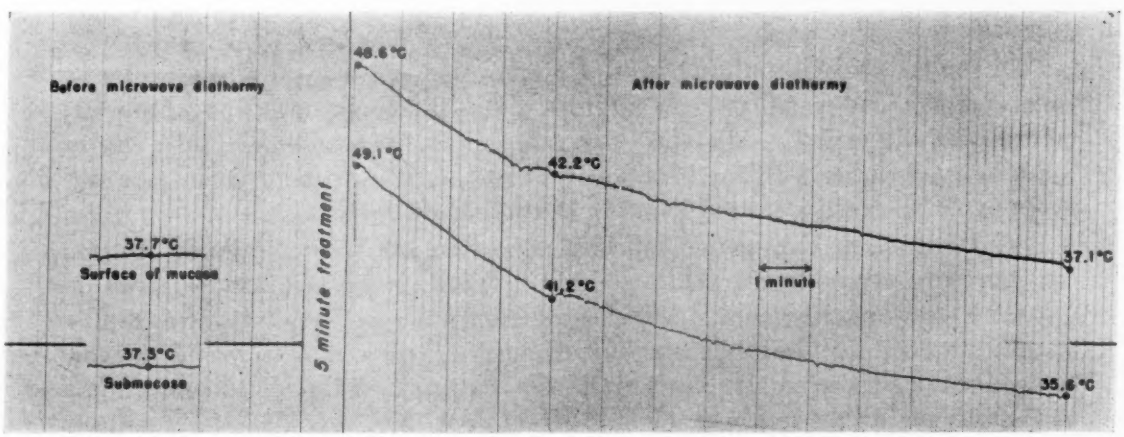

Fig. 4.—Record of temperature changes of mucosa and submucosa induced by microwaves.

The effect of ultraviolet irradiation on the explanted mucosa was determined by the use of an air-cooled quartz mercury vapor arc lamp. The mucosa was exposed on three successive days, respectively, to nine, eighteen, and seventy-two times, the minimal erythemal dose. Twenty-four hours after the third exposure, the mucosa appeared to be dry and damaged extensively. In response to stimulation with histamine, there was only a slight secretion of acid on the upper third of the explant. Forty-eight hours later, however, the mucosa appeared grossly normal, and the entire explant secreted acid.

Ultrasonic waves having a frequency of 800,000 cycles per second from a generator with a maximal output of 15 watts were applied to the explanted mucosa for three hours daily for fourteen consecutive days. On the third day there was a slight hyperemia in the center of the explant. This area corresponded in size and shape to that of the diaphragm of the sound head. No acid

could be demonstrated in this area, although acid was present on the explant on either side of the area. This condition persisted until the termination of this experiment. Microscopic study of this area revealed no destruction of the cells, and one week after the termination of the exposure to ultrasonic waves, hydrochloric acid could be demonstrated over the entire mucosa.

COMMENT

The various methods of studying the gastric mucosa and its secretions were reviewed in an attempt to find a suitable preparation which would permit (1) direct observation of the nature and character of the secretion of the gastric mucosa in response to food or chemical stimulation, (2) direct visualization of the effect of various chemical and physical agents, (3) direct observation of both gross destruction and regeneration of the mucosa by these agents, and (4) biopsy and microscopic study of easily accessible tissue. None was found. Consequently, the early phase of this work was devoted to the development of a satisfactory technique for transplanting a portion of the fundus of a dog's stomach, with its blood supply intact, to the anterior abdominal wall and having this explanted mucosa secrete hydrochloric acid in response to food or chemical stimulation.

Difficulty was encountered in the preparation of some of these explants. Only certain areas would secrete hydrochloric acid in response to food or histamine stimulation. For the most part, this difficulty was eliminated as more technical experience with the preparation was gained, especially when care was taken to choose mucosa located high on the fundus of the stomach.

The possibility that not all parietal cells were active at any one time was considered; attempts were made to block off certain areas of the mucosa on different days but no concrete evidence to support such a hypothesis was found.

Because of the preponderance of evidence to show that it was impossible to decrease the secretion of hydrochloric acid by tying off the main blood supply of the mucosa, an attempt was made to interfere with the capillary blood supply of the glands on the premise that parietal cells, being more specialized, would naturally be more sensitive to any decrease in blood supply. This was the rationale for using Pitressin, protamine, and Hykinone locally. Snake venom, a powerful capillary poison, was considered but discarded because of its obvious toxicity.

A representative group of chemical substances was studied in an attempt to evaluate the claims made by other investigators as to the effect of such chemicals on the secretion of acid. It should be stressed that claims for the production of only a transitory achlorhydria were made in most instances. However, it was felt that the more promising chemicals should be tested, perhaps in stronger solutions. Oil of peppermint, quinone, and the various pituitary extracts were applied directly to the secreting mucosa and all proved to be without significant effect.

There were three outstanding and rather surprising features of this study. The first was the remarkable resistance of this explanted mucosa to the effects

of the local application of the chemical and physical agents used. In this respect our results were similar to those obtained by Wolf and Wolff[10] in their use of injurious agents on the human stomach. The second feature was the protective role played by the rich blood supply of the mucosa. This was best illustrated by the failure to produce significant local changes of temperature by microwaves until the blood supply had been effectively decreased. The same dosage and method of application of these microwaves when applied to the thigh of the dog did produce significant changes of temperature. The third outstanding feature was the extensive regenerative ability of the mucosa from both an anatomic and functional standpoint. The regenerative capacity of many tissues of the body has long been recognized, but perhaps insufficient stress has been placed on the ability of the damaged, practically destroyed, mucosa of the stomach to regenerate, particularly from a functional standpoint.

The gastric mucosa, probably because of the clinical impressions resulting from observations in acute and chronic gastritis, was thought to be more easily injured than these results indicate.

SUMMARY

A portion of functioning gastric mucosa, with its blood supply intact, was brought out through a laparotomy incision and loosely sutured to the edge of the skin of the abdominal wall of the dog. The local application of zinc chloride in 50 per cent solution caused gross and microscopic changes in the mucosa. Application of a 100 per cent solution of zinc chloride produced a necrotizing effect on the mucosa and prevented the secretion of hydrochloric acid for a period of three months. Some regeneration of the gastric mucosa with return of secretion of hydrochloric acid was demonstrable three months after the application of zinc chloride. The local application of Pitressin produced a transitory blanching of the mucosa. Tannic acid, sodium morrhuate, oil of peppermint, protamine, water-soluble vitamin K, quinone, and various pituitary extracts produced no gross, microscopic, or functional changes in the explanted gastric mucosa.

Increasing the body temperature to 108° F. had no demonstrable effect on the ability of the explanted mucosa to secrete hydrochloric acid. A local increase in temperature on the surface and in the submucosa of the explant did not interfere with the secretion of hydrochloric acid. Ultraviolet radiation and ultrasonic radiation produced transient changes in the mucosa.

CONCLUSIONS

1. It is possible to explant a sizable portion of the fundic mucosa of dogs and demonstrate the presence of hydrochloric acid on this explant in response to food or chemical stimulation.

2. Gross, microscopic, and functional changes can be produced by means of various chemical and physical agents.

3. When injury to the mucosa does occur, there is progressive regeneration of the mucosa with gradual return of function, as demonstrated by return of acid-secreting capacity.

4. The gastric mucosa of dogs is remarkably resistant to permanent alterations produced by the chemical and physical agents described.

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THE EXTENT TO WHICH ONE MAY INTERFERE WITH THE BLOOD SUPPLY OF THE ESOPHAGUS AND OBTAIN HEALING ON ANASTOMOSIS

JOSEPH E. MACMANUS, M.D., JOSEPH T. DAMERON, M.D.,* AND JOHN R. PAINE, M.D., BUFFLO, N. Y.

(From the Department of Surgery of the Buffalo General Hospital and the University of Buffalo School of Medicine)

INTRODUCTION

ABOUT 15 per cent of esophageal carcinomas occur at or near the superior thoracic aperture. There is no generally accepted satisfactory technique for the excisions of lesions at this location. To be sure, a few isolated case reports have appeared in the literature describing the excision of lesions at this site with anastomosis of the stomach to the proximal esophagus in the neck.[1, 2] This maneuver, however, would seem to have definite limitations in its applicability.

Some time ago, Dr. Harry Harper suggested to one of us that, if it were possible to preserve a portion of the lower esophagus attached to the stomach, such lesions could be more easily dealt with by passing the distal esophagus through the cervical aperture of the thorax and performing the anastomosis at a convenient level within the neck. The success of such a procedure would depend in large measure on the competence of the collateral blood supply in the wall of the esophagus. The experience of surgeons in attempting to remove lesions of the mid-portion of the thoracic esophagus, during which the esophagus may be freed from practically its entire thoracic bed before the lesion is proved to be inoperable, indicates that the collateral blood supply is much more adequate than has generally been assumed in the past. In such instances, necrosis of the esophagus need not be feared. Swenson's[4] and Parker's[5] recently reported experimental work on dogs further supports this contention.

The best study of the blood supply of the human esophagus with which we are acquainted is that of Rudolph Demel, published in 1924.[6] He found that the arterial blood vessels supplying the esophagus, although subject to frequent minor variations, comprised four main groups as follows.

1.—Vessels supplying the cervical esophagus: Branches from the inferior thyroid arteries and usually a small pair of arteries running directly from the subclavian arteries

2.—Vessels supplying the upper thoracic esophagus (pars bifurcalis-Demel): Anterior and posterior esophageal-tracheal arteries running directly from the aorta

3.—Vessels supplying the lower thoracic esophagus: Small arteries varying in number but arising as pairs from the aorta and

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*United States Public Health Fellow, National Cancer Institute.

known as the anterior and posterior esophageal propria arteries. The arterial supply of this portion of the esophagus is segmental in character

4.—Vessels supplying the abdominal esophagus: Branches of the left inferior phrenic and left gastric arteries

Anastomoses between the vessels of adjacent divisions within the muscular wall of the esophagus were clearly demonstrated. The study of injected and dissected specimens of the dog's esophagus in our own laboratory has shown that the arterial blood supply of the esophagus in this animal is very similar to that in man and has led us to believe that the experiments here reported are of clinical significance.

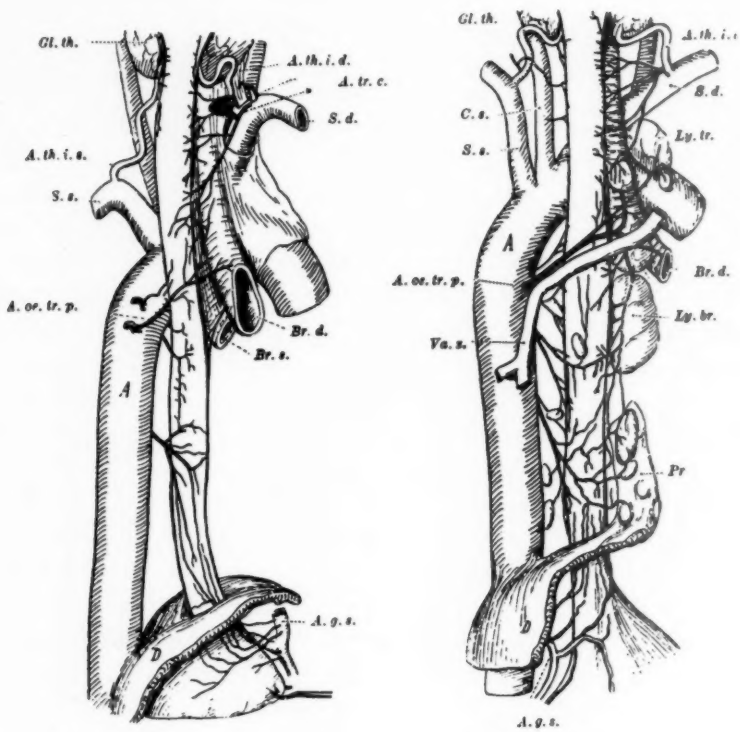

Fig. 1.—Blood supply of the human esophagus (taken from Demel, Arch f. klin. Chir. 128: 453, 1924). *A.th.i.s.*, left inferior thyroid artery; *A.oe.tr.p.*, posterior esophageal tracheal artery; *A.th.i.d.*, right inferior thyroid artery; *A.tr.c.*, transverse cervical artery; *A.g.s.*, left gastric artery; *Pr.*, pericardium.

METHOD OF EXPERIMENTS

Various operations involving the esophagus and stomach were performed upon 46 dogs to determine, first, to what extent the blood supply of the esophagus could be interfered with without producing necrosis, and second, whether or not a significant portion of the distal esophagus could be left attached to the stomach and survive when the stomach was freed from its abdominal attachments by cutting the left gastroepiploic, left gastric, and short gastric vessels and pulled up into the chest.

All animals were operated upon with aseptic technique under Pentothal Sodium anesthesia. Fine silk was used for all sutures and ligatures. When the thorax was opened, respiration was maintained by means of an intratracheal tube connected to an oxygen tank. A small valve* developed during the last war for use by the United States Army Air Force provided rhythmic distention of the lungs at any predetermined pressure.[7] No anesthetist is required, even for prolonged intrathoracic procedures, when this simple device is employed. Intravenous fluid was administered slowly throughout the operation. Initially only an occasional animal was transfused with 300 to 500 c.c. of blood during the operation, but when it became evident that the rather high immediate postoperative mortality was frequently due to shock, transfusion during operation was employed more routinely. After operation, 300,000 units of penicillin in oil was injected intramuscularly daily for three to five days. All animals

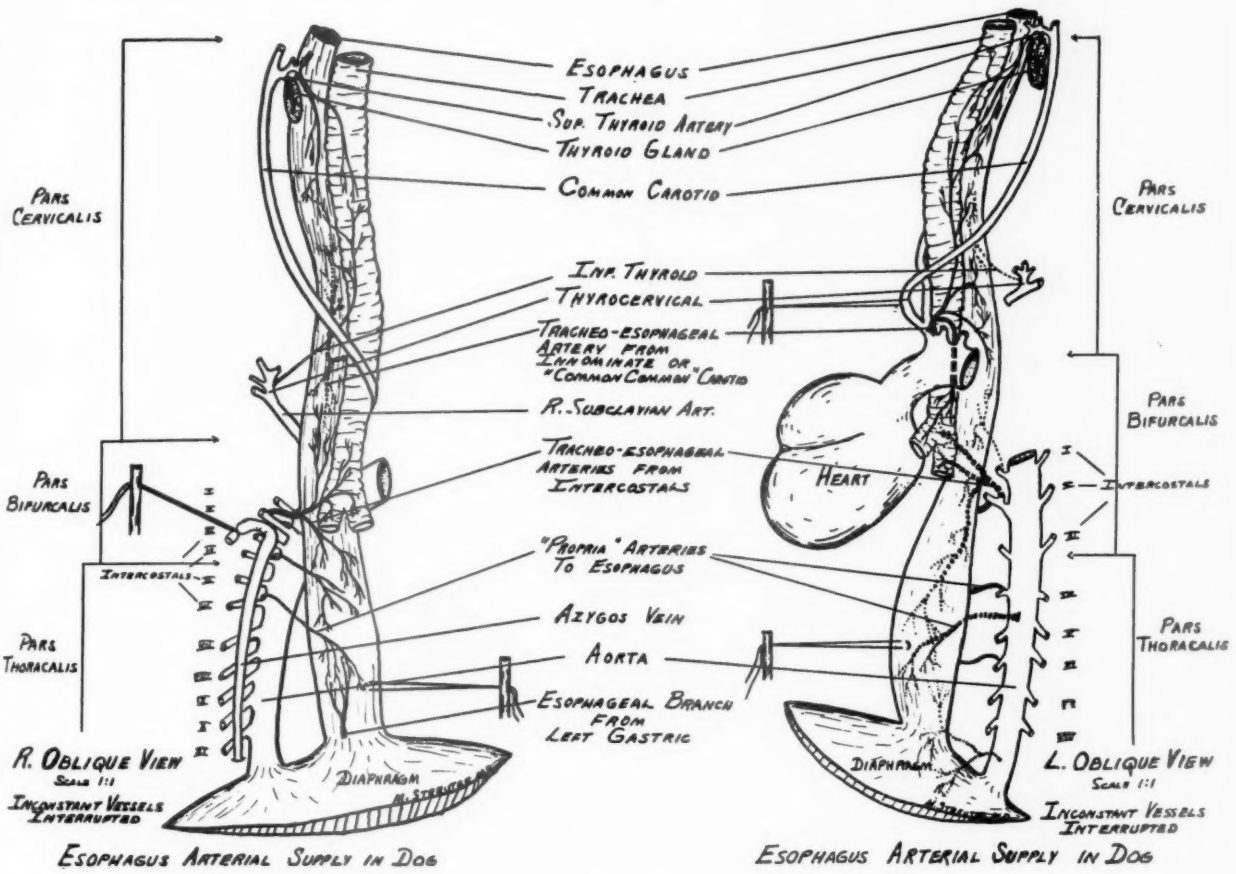

Fig. 2.—Blood supply of dog's esophagus as determined by dissection of injected specimens by Dr. M. A. Streuter.

were allowed to drink water as soon after operation as they wished. On the second postoperative day, they were offered food. A stomach tube was occasionally employed to relieve gaseous distention in those dogs in which the stomach had been brought up into the chest. In some animals a Levine type duodenal tube was inserted through the esophagus and into the stomach at the end of the operation. The proximal end of this tube was brought out through the cheek posterior to the teeth. In this manner it could be kept in place for several days.

*Burns Valve, manufactured by Mine Safety Appliance Company, Pittsburgh, Pa.

RESULTS OF EXPERIMENTS

Five different types of experiments were performed.

The first experiment consisted of devascularizing the entire thoracic esophagus, dividing it, and immediately reanastomosing it. In this procedure a portion of the right fourth rib was excised and the right pleural cavity opened widely. The azygos vein was then divided and ligated on the anterolateral surface of the esophagus. After incising the pleura over the esophagus from the diaphragm to the first rib, the esophagus was raised completely out of its bed and all blood vessels supplying it were divided and ligated. After division at the selected site, anastomosis was performed with two layers of interrupted silk sutures. No clamps were applied to the esophagus at any time. In most instances the vagus nerves were divided incidental to the division of the esophagus. No attempt was made to re-cover the esophagus with pleura. The chest wall incision was closed tightly without drainage.

Eleven dogs were subjected to this procedure. In three, the esophagus was divided at the junction of the lower and middle thirds; in four, at the junction of upper and middle thirds; in four, at about the mid-point of the esophagus just below the level of the azygos vein. Post-mortem examinations were performed in all instances. Necrosis of the esophagus was not observed.

The results of this experiment are summarized in Table I.

TABLE I. DEVASCULARIZATION OF THE THORACIC ESOPHAGUS WITH DIVISION AND ANASTOMOSIS

DOG NUMBER	LENGTH OF SURVIVAL (DAYS)	DEVELOPMENT OF NECROSIS	CAUSE OF DEATH
Anastomosis at Junction of Lower and Middle Thirds			
78	4	None	Empyema
80	183	None	Still living
83	33	None	Sacrificed
Anastomosis at Junction of Upper and Middle Thirds			
82	4	None	Distemper
85	1	None	Shock
86	97	None	Sacrificed
88	153	None	Still living
Anastomosis in Middle Third			
12	1	None	Shock and atelectasis
11	22	None	Sacrificed
21	4	None	Pneumonia
24	80	None	Sacrificed

TABLE II. DEVASCULARIZATION OF THE THORACIC AND CERVICAL ESOPHAGUS

DOG NUMBER	LENGTH OF SURVIVAL (DAYS)	DEVELOPMENT OF NECROSIS	CAUSE OF DEATH
31	68	None	Inanition and vomiting
39	2	None	Shock and atelectasis
37	2	None	Shock
96	5	Hemorrhagic necrosis in esophagus at level T1	Distemper and hemorrhage
102	4	Extensive at level of T2	Sepsis
127	55	None	Still living
111	51	None	Still living
128	6	Extensive at level of T2	Sepsis
104	50	None	Still living

The second experiment consisted of devascularizing the entire thoracic esophagus in the same manner as in the first procedure and, in addition, freeing the cervical esophagus of all of its blood supply. Dissection was extended up to the hypopharynx. The esophagus was not divided.

Two of nine dogs subjected to this procedure died during the first two post-operative days. The remaining seven dogs survived for periods varying from four to sixty-eight days. Three animals developed rather extensive areas of necrosis in the esophagus at the level of the second thoracic vertebra and died between the fourth and sixth days after operation.

Fig. 3.

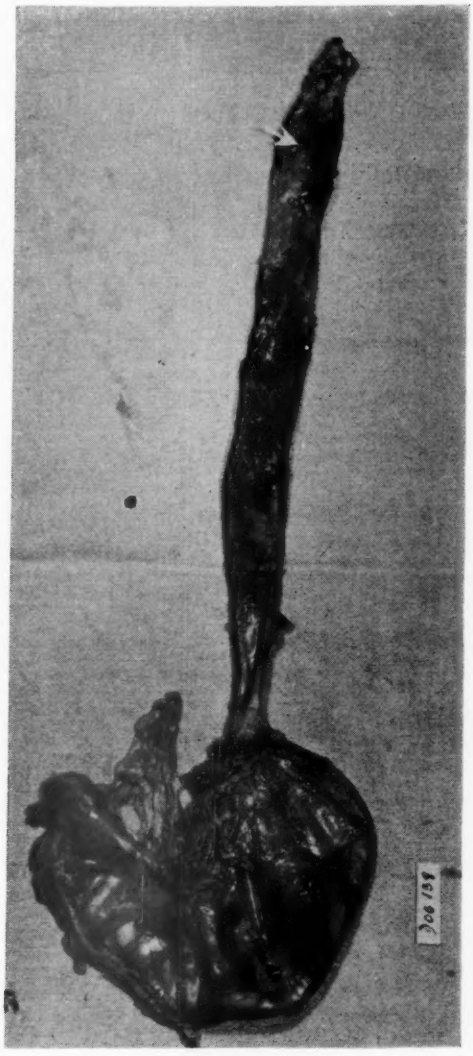

Fig. 4.

Fig. 3.—Post-mortem specimen of esophagus of Dog 128. This extensive necrosis of the upper thoracic esophagus followed complete devascularization of the thoracic and cervical esophagus.

Fig. 4.—Post-mortem specimen of the entire esophagus and stomach of Dog 139. Devascularization of the entire esophagus and stomach resulted in necrosis and perforation of the mid-cervical esophagus (indicated by arrow). The tissues of the upper thoracic esophagus were infiltrated with blood, but no actual necrosis was present.

TABLE III. DEVASCULARIZATION OF THE STOMACH, ABDOMINAL ESOPHAGUS, THORACIC ESOPHAGUS, AND CERVICAL ESOPHAGUS

DOG NUMBER	LENGTH OF SURVIVAL (DAYS)	DEVELOPMENT OF NECROSIS	CAUSE OF DEATH
89	6	At level T4	Sepsis perforation
92	50	None	Inanition
130	2	Entire lower ½ of thoracic esophagus	Shock
132	6	At level C6	Sepsis
123	5	At level T1	Sepsis
138	1	None	Shock & atelectasis
139	1	Entire lower ⅓ of thoracic esophagus	Shock; stomach with blood

The results of this experiment are summarized in Table II.

The third experiment consisted of devascularizing the cervical esophagus, the thoracic esophagus, the abdominal esophagus, and the stomach. This extensive operation was performed through three incisions. A left paramedian abdominal incision was used to free the stomach from all of its blood supply

TABLE IV. DEVASCULARIZATION OF THE STOMACH, ABDOMINAL ESOPHAGUS, AND THORACIC ESOPHAGUS, WITH DIVISION* AND ANASTOMOSIS WITHIN THE THORAX

DOG NUMBER	LENGTH OF SURVIVAL (DAYS)	DEVELOPMENT OF NECROSIS	CAUSE OF DEATH
28	5	None	Dilatation of stomach
93	43	None	Sacrificed
40	27	None	Dilatation of stomach
44	1	None	Shock

*Esophagus was divided in the middle one-third of the thoracic esophagus.

except the right gastric and right gastroepiploic arteries at the pylorus. Great care was used to preserve intact the arch of the gastroepiploic artery along the greater curvature of the stomach. The left gastric artery, the left gastroepiploic artery, and the vasa brevia were ligated close to their origins. The abdominal

TABLE V. RESECTION OF THE UPPER THORACIC AND LOWER CERVICAL ESOPHAGUS, TRANSPLANTATION OF THE STOMACH INTO THE CHEST, AND ANASTOMOSIS OF THE REMAINING PORTIONS OF THE ESOPHAGUS

DOG NUMBER	LENGTH OF SURVIVAL (DAYS)	DEVELOPMENT OF NECROSIS	CAUSE OF DEATH
49	1	None	Shock; tension pneumothorax
67	1	None	Shock
71	1	None	Shock
116	1	None	Tension pneumothorax
120	1	None	Tension pneumothorax
121	2	None	Atelectasis
118	2	None	Aspiration of gastric contents
70	1	None	Acute gastric dilatation
50	30	None	Acute gastric dilatation
16	10	None	Cervical abscess
117	4	None	Sepsis chest wall infection
119	32	None	Acute gastric dilatation
122	46	None	Acute gastric dilatation
129	44	None	Acute gastric dilatation and emaciation

esophagus was dissected free and also severed from its diaphragmatic attachments. In most instances the spleen was excised incidental to the aforementioned procedure.

After closure of the abdominal incision, the right chest was opened and the thoracic esophagus dissected completely free as in the previous procedures. After the thoracic incision was closed the cervical portion of the esophagus was devascularized through a third incision.

Fig. 5.—Injected arteries of the lower esophagus of Dog 93. Injection of a radiopaque mass was made through the left gastric artery when the animal was sacrificed forty-three days following devascularization of the stomach, abdominal esophagus, and thoracic esophagus, followed by division and anastomosis of the thoracic esophagus. The white marker indicates the level of the superior thoracic aperture. Note the healed anastomosis below.

Seven dogs survived this prolonged and extensive procedure, but one of them died of shock and atelectasis twelve hours after operation. Two others died the second postoperative day. The post-mortem examination of these two animals revealed that the cardiac portion of the stomach had herniated through the defect remaining in the diaphragm after the esophagus was severed from its diaphragmatic attachments. The lower one-third of the thoracic esophagus and

the herniated portion of the stomach in both instances were involved in hemorrhagic necrosis due to strangulation. Three of the remaining four animals died on the fifth and sixth postoperative days with necrosis and perforation of the esophagus. The remaining animal survived fifty-one days to die of inanition after prolonged vomiting. The post-mortem examination showed very marked dilatation of the esophagus and stomach.

The results of this experiment are summarized in Table III.

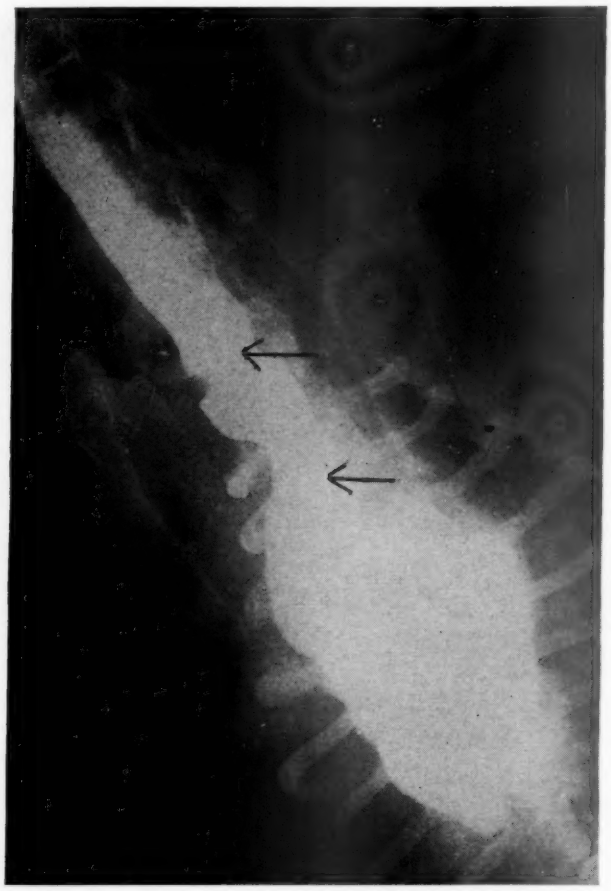

Fig. 6.—Roentgenogram of Dog 119 taken four weeks following resection of the upper thoracic and lower cervical esophagus with transplantation of the stomach into the chest and anastomosis of the remaining portions of the esophagus. The arrows indicate the level of the esophageal anastomosis and the cardia of the stomach.

The fourth experiment consisted of devascularizing the stomach, abdominal esophagus, and thoracic esophagus in the manner previously described. In addition, the esophagus was divided in the thorax at approximately the level of the azygos vein and immediately anastomosed as just described.

Four animals were used in this experiment. One died of shock on the first postoperative day. The other three survived for five to forty-three days. None showed necrosis of the esophagus at post-mortem examination.

The results of this experiment are summarized in Table IV.

The last experiment consisted of resection of that portion of the esophagus extending from the level of the azygos vein to the mid-cervical region and anastomosis of the two remaining portions of the esophagus. To accomplish this, three incisions were employed as in the third procedure and the stomach was pulled up into the chest after being freed of its blood supply and abdominal

Fig. 7.

Fig. 8.

Fig. 7.—Post-mortem specimen of the entire esophagus and stomach of Dog 119. Death occurred thirty-two days after the anastomosis was made.

Fig. 8.—Injected arterial network of the esophagus of Dog 119. Injection was made through the left gastric artery. The injection mass had passed across the line of anastomosis indicated by the arrow.

attachments except at the pylorus. That portion of the thoracic esophagus left attached to the stomach measured four to seven inches, depending upon the size of the dog. This portion of the esophagus was passed up through the superior aperture of the chest and the anastomosis made in the neck. In addi-

tion, the proximal portion of the cervical esophagus was freed of its blood supply except for collateral vessels entering from the hypopharynx.

Fourteen dogs were used for this experiment. Eight of these animals died during the first three postoperative days. The remaining six survived for four to forty-six days. All animals were subjected to post-mortem examination. Necrosis of the esophagus or stomach was not found.

The results of this experiment are summarized in Table V.

Fig. 9.—Photomicrograph of esophageal wall at line of anastomosis in Dog 119, thirty-two days after operation.

DISCUSSION

The relatively high immediate mortality associated with all the procedures used in these experiments is striking but not surprising. For obvious reasons it is impossible to utilize in the experimental laboratory all the supportive and protective measures that experience has shown are necessary to carry out major operative procedures on the esophagus in the human patient with an acceptable mortality rate. Furthermore, it is well known that the dog in particular withstands interference with the vagal innervation of the stomach and esophagus poorly. Some investigators have felt that severance of both vagus nerves high in thorax will inevitably produce death in the dog. This is probably not strictly true, but in the majority of cases death will occur sooner or later from one of a number of causes.[8]

Surgical shock and varying degrees of atelectasis accounted for most of the immediate postoperative deaths. All of the animals had some interference with the vagal nerve supply of the upper gastrointestinal tract and in most of them

there was a complete division of both vagus nerves within the thorax. The altered physiology of the esophagus and stomach thus produced accounted for most of the remaining deaths. Dilatation of the esophagus and stomach associated with emesis was a marked feature of those animals surviving the immediate postoperative period. The fact that most of the experimental animals died eventually, however, did not vitiate the value of the experiments. Gangrene or necrosis consequent to an inadequate blood supply should have made itself evident rather quickly in cases where the diminution in the blood supply was accomplished quickly.

We have assumed that those animals not surviving operation for three days could not be considered in evaluating the liability of the operative procedure to cause necrosis of the esophagus. However, if signs of necrosis had been present in any of the animals dying within three days after operation, such signs would have been significant. For the sake of completeness, all the animals operated upon have been included.

The results obtained in the first experiment definitely confirm Parker's results. The collateral blood-pathways in the wall of the esophagus are sufficient to maintain viability of tissue and to insure healing of an anastomosis when the entire thoracic blood supply to this organ has been severed. The capacity of this intrinsic blood vessel network, however, does have a limit. It is not surprising that three out of seven dogs surviving devascularization of the thoracic and cervical esophagus by more than three days should develop necrosis and perforation. It is significant, however, that in each instance necrosis and perforation occurred at approximately the same level, namely that of the second thoracic vertebra. Demel's anatomic studies of the human esophagus as well as our own studies of the dog's esophagus indicate that this transition zone between the cervical and thoracic esophagus has the poorest blood supply of any part of the organ. When devascularization of the stomach, except for the right gastric and right gastroepiploic arteries, was added to complete devascularization of the abdominal, thoracic, and cervical esophagus, necrosis occurred in all but one animal. Dogs 139 and 130 are special instances in which the collateral blood flow from the stomach was shut off incidental to the herniation of the stomach through the diaphragm. The necrosis which occurred in the other dogs was all above the level of the azygos vein. From this fact it could be tentatively assumed that the collateral blood flow to the esophagus from the partially devascularized stomach is sufficient to protect the lower two-thirds of the thoracic esophagus from necrosis. The results of the fourth experiment give further support to this contention. None of these animals developed necrosis when division and anastomosis were added to devascularization.

In the fifth experiment necrosis of the esophagus distal to the level of the azygos vein did not occur in any animal. It would, therefore, seem feasible from the standpoint of tissue viability that, in patients in whom the excision of esophageal lesions requires the transplantation of the stomach into the chest, sizeable portions of the distal esophagus may be left attached to the stomach

if the surgeon desires when the continuity of the upper gastrointestinal tract is being re-established. Such instances might occur in cases of tumors or strictures of the upper esophagus or in cases of tracheo-esophageal fistula.

Further studies concerning the function of the distal segment of the esophagus following its denervation and devascularization, however, must be made before such a procedure as that described can be fully recommended. We have been impressed by the rather consistent dilatation of the esophagus which follows its devascularization, denervation, division, and anastomosis. The concomitant dilatation of the stomach seen in the dog is probably of less importance, since experience has shown that the human stomach, when transplanted into the chest following excision of the distal esophagus, is capable of satisfactory function. Additional studies are being made at the present time to learn more about this problem.

SUMMARY

Five different operations have been performed upon a total of forty-six dogs in an attempt to determine to what extent the blood supply of the esophagus must be compromised to produce necrosis of this organ, and whether or not a significant portion of the distal esophagus may be left attached to the stomach and survive when the latter organ is transplanted into the thoracic cavity.

The immediate mortality following all of these operations was high.

Nine of eleven dogs survived complete devascularization, division, and anastomosis of the thoracic esophagus, by more than three days. None developed necrosis.

Seven of nine dogs survived complete devascularization of the thoracic and cervical esophagus without division by more than three days. Three of these animals developed necrosis at approximately the level of the second thoracic vertebra.

Four out of seven animals survived devascularization of the stomach, abdominal esophagus, thoracic esophagus, and cervical esophagus without division by more than three days. Three of these animals developed necrosis between the level of the sixth cervical vertebra and the fourth thoracic vertebra.

Four out of five animals survived devascularization of the stomach, abdominal esophagus, and thoracic esophagus with division and anastomosis within the thoracic cavity by more than three days. None developed necrosis.

Six out of fourteen animals survived resection of the upper third of the thoracic and lower cervical esophagus, transplantation of the stomach into the chest, and anastomosis of the remaining portions of the esophagus within the neck by more than three days. None developed necrosis.

Dogs exhibited consistent dilatation of the esophagus as well as the stomach following procedures designed to decrease the blood supply of these organs and which incidentally produce varying degrees of denervation.

CONCLUSIONS

1. The collateral blood flow within the walls of the esophagus is more adequate than previous opinion has allowed.

2. Necrosis of the dog's esophagus does not occur following complete devascularization of the thoracic portion, division, and anastomosis.

3. Complete devascularization of the dog's thoracic and cervical esophagus usually produces necrosis of the upper thoracic esophagus.

4. Partial devascularization of the dog's stomach and complete devascularization of the abdominal esophagus, thoracic esophagus, and cervical esophagus usually produces necrosis of the upper thoracic esophagus.

5. Studies on a relatively small number of dogs indicate that the stomach and that portion of the distal thoracic esophagus below the level of the azygos vein can be transplanted upward and an esophageal anastomosis performed at a convenient level in the neck without fear of necrosis of the esophagus.

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STUDIES ON AN ANTITHROMBIN

III. A Plasma Antithrombin Test for the Prediction of Intravascular Clotting

John H. Kay, M.D., Samerill B. Hutton, Jr., M.D., Gerald N. Weiss, M.D., and Alton Ochsner, M.D., New Orleans, La.

(From the Department of Surgery, Tulane University School of Medicine)

PHLEBOTHROMBOSIS and the embolism which sometimes follows it are still playing a considerable role in postoperative morbidity and mortality. For many years both the incidence of these conditions and the death rate associated with them remained fairly constant. Then, during the past two decades, the use of pressure bandages, early ambulation, and similar precautions began to reduce the incidence of phlebothrombosis, while prophylactic and postphlebitic venous ligation began to reduce the mortality of embolism. The prophylactic use of anticoagulant agents has also played a part in the improvement, but this form of therapy is potentially dangerous. The hemorrhagic diathesis which occasionally results is always dangerous and may be fatal.

Our studies on postoperative clotting began with an investigation of the normal process of coagulation. The complete mechanism of this process is still to be clarified, but we did make one significant observation. There is apparently no method for the conversion of fibrinogen to fibrin which has good tensile strength except by the use of thrombin. The degree of cohesiveness of the resulting clot is a function, at least in part, of the amount of ionized calcium present in the substrate.[1]

These observations suggest that phlebothrombosis cannot occur until more or less thrombin is formed intravascularly. They also suggest, since intravascular clotting does not occur after every operation, that while some thrombin must be released into the blood stream at every operation, under normal circumstances it is inactivated by a circulating antithrombin with which it combines. Additional studies, which have been reported elsewhere, indicate that this circulating antithrombin may be alpha tocopherol phosphate, which is normally present in the alpha globulin and gamma globulin fractions of the blood. Finally, our studies have shown that fibrinogen B is a complex which is composed of thrombin, antithrombin, and fibrinogen.[2]

The investigations carried out by Cumine and Lyons[3] showing that fibrinogen B is present in patients who develop postoperative thrombosis permit another conclusion: the appearance of fibrinogen B in the blood of such patients may represent a fall in the plasma antithrombin, which is no longer free because it has combined with thrombin.

CLINICAL STUDIES: SERIES A

In an attempt to test the clinical applicability of these observations, studies were carried out on an unselected, consecutive series of patients submitted to major surgical procedures, the investigations including plasma antithrombin

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levels, prothrombin times, fibrinogen B levels, and clotting times. These values were determined in 120 surgical subjects on the day before operation and for periods ranging from 5 to 12 days after operation. Similar studies were begun in 34 other patients but for one reason or another were not completed and are therefore not reported, though it might be well to add that no one in the group developed any evidence of intravascular clotting.

Technical Methods

Plasma Antithrombin Determination.—Since no method was already available to measure the antithrombin level of the plasma, the following technique was devised:

1. Place in a test tube 1.4 ml. of 1.85 per cent solution of $K_2C_2O_4$ (potassium oxalate).
2. Add 10 ml. of blood as soon as it is withdrawn and mix well.
3. Centrifuge at 1,500 r.p.m. for 10 minutes.
4. Remove the supernatant plasma.
5. Make a serial dilution of the plasma as follows.
   (a) Place 0.5 ml. of plasma in tube No. 1.
   (b) Place 0.5 ml. of plasma in tube No. 2, add 0.5 ml. of distilled H_2O and mix well (1:2).
   (c) Place 0.5 ml. of the mixture from tube No. 2 in tube No. 3, add 0.5 ml. of distilled H_2O and mix well (1:4).
   (d) Continue to dilute the plasma in the manner described until 10 tubes have been prepared. The dilution in the tenth tube is 1:512.
6. Add to each tube exactly 0.1 ml. of thrombin solution. This solution* is put up in 65 unit ampules. Each cubic centimeter contains 0.01 units of thrombin in the final dilution.
7. Shake the tubes well, then incubate them in a water bath at 37.6° C. for 30 minutes.
8. Add to each tube 0.1 ml. of 3 per cent bovine fibrinogen† solution, from which profibrin has been removed by freezing. Shake well.
9. Incubate the tubes for 60 minutes.
10. Observe each tube for clot formation, recording the greatest dilution at which it ceases to occur. In normal plasma clot formation ceases to occur when the plasma dilution is between 1:32 and 1:128.

Plasma Antithrombin Test: Recently a simpler, quicker plasma antithrombin test has been developed.‡ The technique is as follows. The principle of this test is based on the knowledge that each plasma contains enough antithrombin to inhibit a specific amount of thrombin, and that clotting occurs only when this amount of thrombin is present.

1. One-half milliliter of plasma is placed in each of 5 tubes.
2. Thrombin solutions are prepared in the following manner. At the beginning of each week one ampule of Thrombin Topical§ is opened and prepared so that each milliliter contains 100 units per milliliter in distilled water.‖ The thrombin can be kept frozen for one week and must then be discarded. When the test is to be run, 1 ml. is melted at 37° C. and diluted so that is contains 1 unit per milliliter. Five dilutions are then made as follows. From the 1 unit per milliliter dilution take: 0.4 ml., add 9.6 ml. distilled water; 0.8 ml., add 9.2 ml. water; 1.6 ml., add 8.4 ml. water; 3.2 ml., add 6.8 ml. water; 6.4 ml., add 3.6 ml. water. These dilutions compare with the 1:4, 1:8, 1:16, 1:32, and 1:64 values of the old test. Then 0.1 ml. of the different concentrations is added to a 0.5 ml. plasma aliquot and clot formation read after 15 minutes' incubation at 37° C.

*Specially prepared by Parke, Davis & Co., Detroit, Mich.
†The Armour Laboratories, Chicago, Ill.
‡By Dr. George Balla.
§Parke, Davis & Co., Detroit, Mich.
‖The exact amount of thrombin in each ampule originally can be determined only by contacting Mr. Eugene Loomis, Parke, Davis Research Laboratories, Detroit 32, Mich.

The end point is taken as the last tube containing a clot. Because of the antithrombic activity of the fibrinogen used in the former test, this shift of the end point gives readings identical with those obtained with the other test.

The end points are very clear-cut. Occasionally a flake of protein can be seen but this microscopically does not show fibrin strands and will introduce error if read as clot formation. Only the strandlike fine fibrin clot is used as an end point.

Fibrinogen B Determination.—The fibrinogen B test was performed by the following technique.

1. Prepare a 2 per cent solution of β-naphthol in alcohol by combining 0.4 Gm. of β-naphthol with 20 c.c. of 50 per cent alcohol.
2. Let this solution stand in the air for 24 hours.
3. To 1 c.c. of oxalated plasma add 5 drops of 2 per cent solution of β-naphthol.
4. Let stand for 15 minutes.
5. Observe for gel formation recording degree as 0, 1+, 2+, 3+, and 4+.

Prothrombin Time Determination.—The Quick method for determination of the prothrombin time was used. Lung thromboplastin* consistently gave a 14 to 16 second normal. More recently we have used a mixture of brain and lung thromboplastin† which is stable in solution at 4° C. for several weeks. This also gives a normal of 14 to 16 seconds.

The two-stage method for prothrombin time did not prove satisfactory for the purposes of this study. When the one-stage and two-stage methods were both used in the same case it was found that the Quick method was apparently influenced by changes in the rate of conversion of prothrombin, so that normal or near normal values were obtained at times when the absolute level of prothrombin units were low. For this reason the Quick method appears to be of value in predicting phlebothrombosis while the two-stage method, as generally used, is not. It is possible to measure rate of conversion by the two-stage method, but the one-stage method is simpler and seems adequate.

When the one-stage method is used, it is important that clot formation, and not the first appearance of fibrin, be used as the end point. Our work suggests that the first fibrin which appears may be calcium-alpha tocopherol-fibrinogen complex while the clot produced by thrombin is a solid gel, with good tensile strength but with little cohesiveness.

Clotting Time Determinations.—Clotting times were determined on venous blood by means of the capillary tube method.

Results

1. Fibrinogen B determinations were made in 87 patients, in 75 of whom this substance was present in the blood at some time during the postoperative period. Of the 75 patients in whom it was present, 13 had clinical evidence of thrombosis or embolism.

2. In 48 of the 75 patients with fibrinogen B in their blood determinations of the clotting time were made concomitantly with fibrinogen B determinations during the postoperative period. Fibrinogen B was present, and the clotting time was 3 minutes or less on the same postoperative day, in 19 of the 48. Five of the 19 presented clinical evidence of intravascular clotting, but so also did 4 of the 29 patients whose clotting time was higher than 3 minutes.

CLINICAL STUDIES: SERIES B

Since these results clearly indicated that determinations of fibrinogen B and of the clotting time do not provide an efficient means of identifying pa-

*Supplied by The Maltine Company, Morris Plains, N. J.
†Supplied by E. W. Blanchard of Schieffelin & Company, New York, N. Y.

tients likely to develop intravascular clotting, the following additional studies were carried out.

Antithrombin levels and prothrombin times were determined daily after operation in 120 unselected cases. In all of these patients major surgical procedures had been performed. The tests were discontinued after the fifth day in patients whose antithrombin levels were 1:32 or higher. If the antithrombin values were below this level, the daily determinations were continued until they had become 1:32 or higher and until fibrinogen B had been absent from the blood for 3 successive days. These criteria were selected arbitrarily, it is true, but they have proved satisfactory in that no clinical evidence of intravascular clotting appeared in any of these cases after the daily determinations had been discontinued.

Results

Of the 120 patients studied, 53 had antithrombin levels of 1:16 or less at some time during the postoperative period. Of these 53, 30 had prothrombin times longer than 20 seconds (15 seconds being regarded as normal), and 23 had prothrombin times shorter than 20 seconds, on the days that their antithrombin levels were 1:8 or 1:4.

Of the 23 patients with these values, 13 developed clinical evidence of thrombosis or embolism. Only 1 of the 20 patients who simultaneously had prothrombin times above 20 seconds and antithrombin levels of 1:8 or 1:4 presented any clinical evidence of intravascular clotting. This patient died of cerebral thrombosis; when the intravascular clot became evident, the antithrombin level was 1:4 and the prothrombin time 39 seconds. Of 7 other patients who died, all of causes other than embolic, 6 had prothrombin times above 20 seconds and antithrombin levels of 1:8 at the same time.

None of the 67 patients whose antithrombin levels were above 1:16 presented evidence of thrombosis or embolism. The single death in this group was the result of other causes.

THE CLINICAL USE OF ALPHA TOCOPHEROL

In 4 cases of thrombophlebitis (not included in the series already described) in which antithrombin levels of 1:8 or 1:16 were found, the oral administration of alpha tocopherol* in doses of 100 International Units 3 times daily raised the levels to 1:64. Simultaneously with this elevation the inflammation subsided and the edema disappeared. In all cases in which alpha tocopherol was injected (in a preparation of sesame oil) there was a preliminary drop in the antithrombin level, with a subsequent rise. The preliminary drop was sometimes pronounced, which suggests that this method should not be employed in any patient whose antithrombin level is already dangerously low.

In a group of 99 patients alpha tocopherol acetate was administered orally in doses of 200 International Units every 8 hours postoperatively. In this group, 17 patients showed antithrombin levels of less than 1:16 and there were 3 cases of thromboembolism.

*In the form of Epsilan-M, supplied by The Warren-Teed Products Co., Columbus, Ohio.

In vitro studies indicate that tocopherol is one of 3 components of the normal plasma antithrombin and calcium is a second. Tocopherol alone will not consistently raise and maintain the antithrombin level. In a series of 50 postoperative cases we have been able to maintain the antithromin levels by the use of 200 International Units of alpha tocopherol every 8 hours and 10 c.c. of 10 per cent calcium gluconate intravenously every 24 hours. There has been no thromobembolism in this group; however, statistical proof awaits a longer series of cases.

SUMMARY AND CONCLUSIONS

1. Alpha tocopherol, which is a potent inhibitor of thrombin, occurs in the accelerator globulin fraction of plasma and in Cohn's fraction I.

2. When antithrombin in this form is combined with fibrinogen and thrombin in optimum quantities, a substance is formed which is chemically indistinguishable from fibrinogen B. Studies with both substances indicate that they are identical.

3. Determinations of the plasma antithrombin levels in clinical subjects submitted to major surgery suggest that thrombosis is likely to occur in the postoperative period when the plasma antithrombin level is abnormally low while at the same time the prothrombin conversion rate is at, or near, normal.

4. Studies in a small group of patients suggest that the antithrombin level can be raised by the oral administration of alpha tocopherol and the intravenous administration of calcium gluconate.

The use of plasma antithrombin determinations to identify patients in whom intravascular clotting may be expected to occur would place on hospital laboratory facilities a burden out of proportion to the clinical value of the method. To identify the small number of patients in this category (not more than one-half of the small number with low values who simultaneously show a normal prothrombin time), it would be necessary to perform both tests every day for at least 5 days on all postoperative patients. From this standpoint, the work which has been reported in this communication is chiefly of theoretical value. On the other hand, the results of these studies give rise to the hope that the routine administration of alpha tocopherol and calcium in the postoperative period may eventually prove to be the means of eliminating intravascular clotting as a postoperative complication.

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AN EXPERIMENTAL STUDY OF REGIONAL HEPARINIZATION

EDWIN J. WYLIE, M.D., RICHARD E. GARDNER, M.D., ROBERT JOHANSEN, M.D., AND H. J. MCCORKLE, M.D., SAN FRANCISCO, CALIF.

(From the Division of Surgery and Laboratory of Experimental Surgery, University of California Medical School)

THE value of anticoagulant therapy used in association with arterial embolectomy has become well recognized in recent years. Heparin used alone or in conjunction with Dicumarol has extended the period of operability, decreased the vascular complications, and in many instances saved an extremity which would otherwise have had to be amputated. A method for continuous local intra-arterial infusion of heparin has been devised in order to facilitate its administration and avoid complications inherent in the systemic administration of anticoagulants. The therapeutic implications of such a method are demonstrated by the experimental data. One case is described to illustrate the clinical application of these studies.

METHOD

Experiments were done on five mongrel dogs with an average weight of 11 kg. Intravenous sodium pentobarbital was used for anesthesia. The femoral artery and vein of each leg were exposed under aseptic surgical conditions. Blood samples were taken from one femoral vein at the beginning of each experiment and coagulation times were measured as a control. All coagulation times were determined by the Lee-White method. A purse-string suture of 00000 Deknatel was then placed in the superficial layers of the anterior surface of one femoral artery, care being taken not to puncture the intima. Through a minute incision in the center of this suture, one end of a Polythene tube with an inside diameter of 0.015 inch was introduced into the artery and the suture was tightened (Fig. 1). A No. 20 hypodermic needle was inserted in the opposite end and connected to a flask containing heparin in normal saline solution in a concentration of 4 mg. per 100 c.c. The dilute heparin solution was allowed to drip into the artery at uniform rates during the course of the experiment. It was necessary to utilize a pressure reservoir to overcome the arterial pressure. Blood samples were taken from each femoral vein at regular intervals and coagulation times recorded.

RESULTS

Inasmuch as previous experimental and clinical work has demonstrated that a coagulation time of fifteen minutes is adequate to prevent local thrombosis after the removal of an embolus,[3, 11, 20] the infusion of heparin into the artery was adjusted to a rate sufficient to maintain this level in the corresponding femoral vein. Figs. 2 and 3 serve to illustrate the series. The infusion of heparin at an average rate of 30 drops per minute prolonged the coagulation time of the blood in that extremity to approximately fifteen minutes (Fig. 2). During the two-hour period of this experiment, the coagulation time of the op-

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posite leg did not increase more than three minutes above its normal value. The initial infusion of heparin at too rapid a rate gave an immediate systemic effect, but when the rate was reduced, the coagulation time of the control extremity returned to normal and an adequate prolongation of the coagulation time persisted in the infused extremity (Fig. 3).

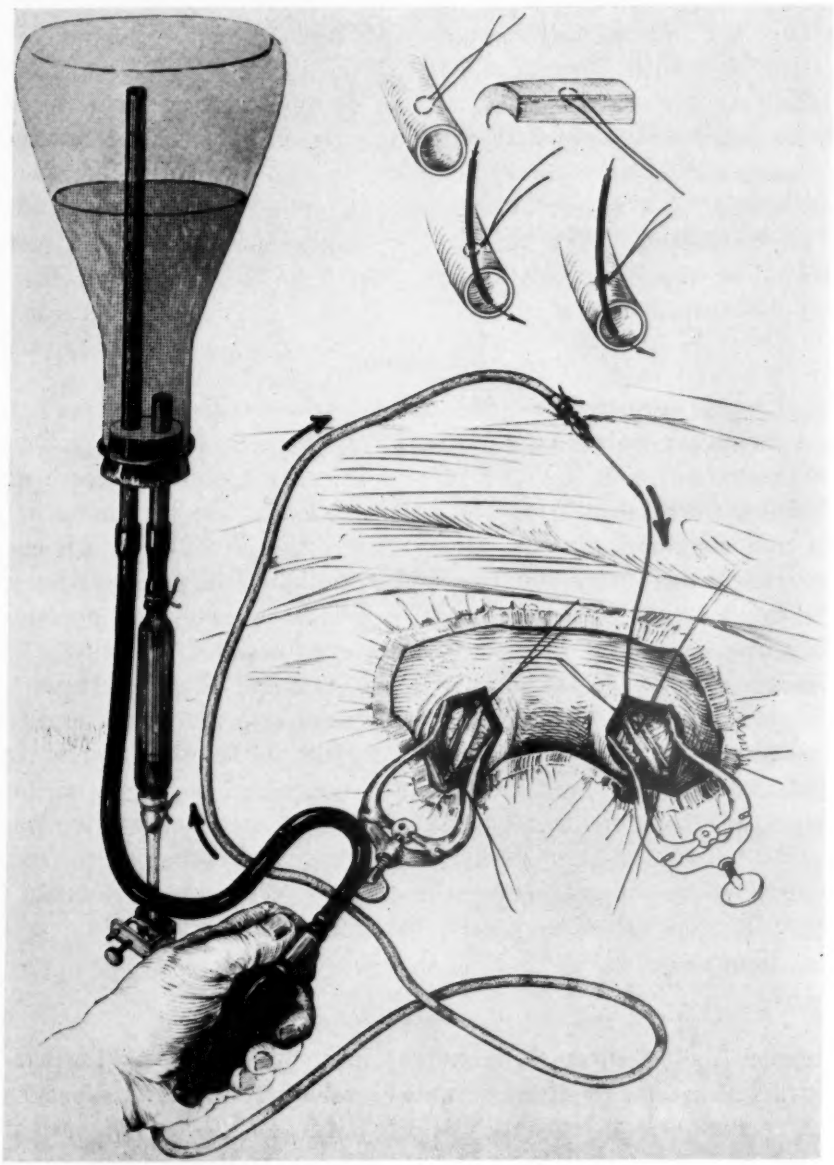

Fig. 1.—Diagram indicating method of local intra-arterial heparinization in the femoral artery of dogs.

Data from the other three animals paralleled these and demonstrated that by controlling the rate of heparin flow, adequate anticoagulant levels could be maintained locally without a systemic effect.

Similar studies were done on two other dogs, and coagulation times were also determined on blood specimens taken from the inferior vena cava and the heart. The normal coagulation time of the blood from the right auricle indicated

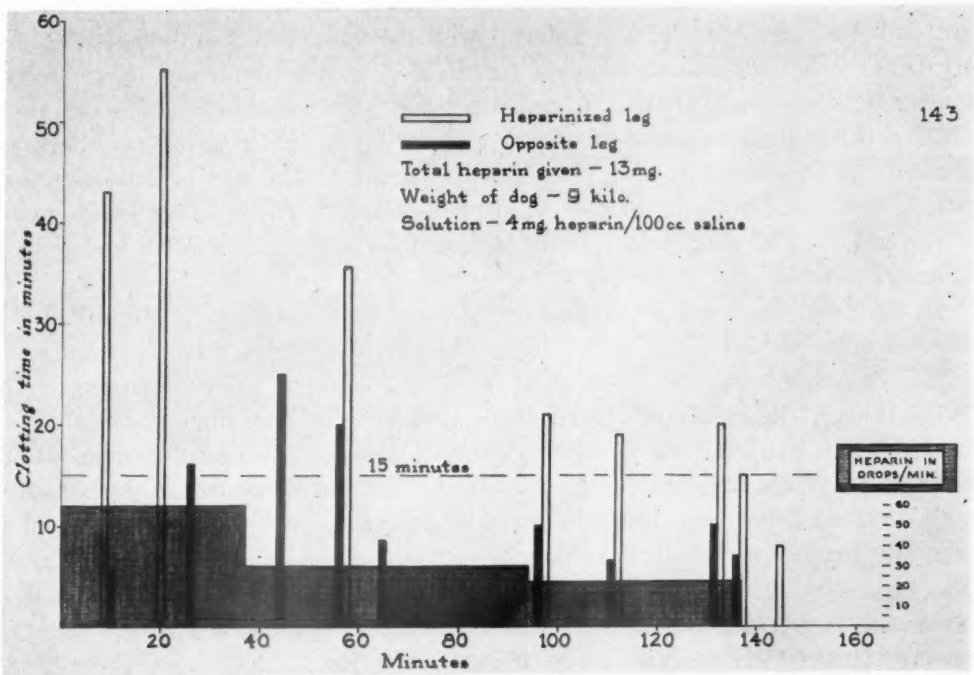

Fig. 2.

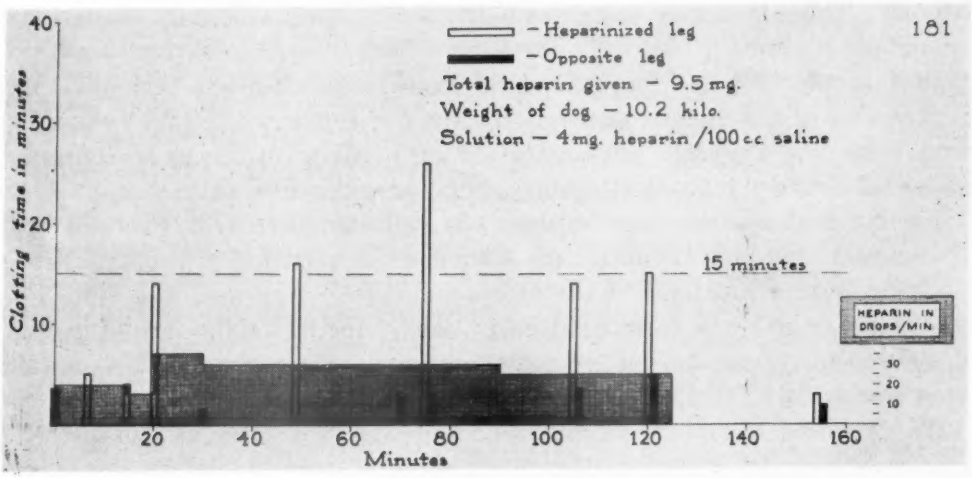

Fig. 3.

Figs. 2 and 3.—Graphs demonstrating comparison of clotting time of blood in the heparinized extremity and the remaining systemic circulation of dogs.

that the dilution by venous blood in the inferior vena cava and from the superior vena cava was sufficient to restore the normal clotting mechanism.

Unusual bleeding from the operative wound was noted only in those instances in which heparin was given at a rate sufficient to induce systemic effects.

DISCUSSION

A review of the pathologic processes which occur at the time of and following the occurrence of an embolus in a major artery to an extremity suggests the therapeutic possibilities of this method of regional heparinization. At the site of an embolus, all layers of the arterial wall become acutely inflamed within a short time. The intimal damage is manifested in the tendency to recurrent thrombosis after removal of the embolus.[4, 9, 16] The incidence of local postoperative thrombosis increases in direct proportion to the time interval between lodgement of the embolus and its removal. Prior to the use of anticoagulant therapy, this complication usually made embolectomy futile after many hours had elapsed.[17] The results of embolectomies done more than twelve hours after lodgement were almost uniformly poor.[5, 7, 15, 22]

In addition to the local process, impairment of the lumina of the distal and collateral arterial tree rapidly develops. The local arterial insult provokes immediate vasoconstriction with retardation of the blood flow in all vessels in the affected limb. The resultant anoxia leads to diffuse intimal damage which initiates a distally propagating thrombus extending from the embolus into all the ramifications of the arterial tree.[1, 2, 6, 10, 11, 12] The results from the experimental use of heparin following closure of arterial incisions, and following removal of artificially produced emboli, have demonstrated the low incidence of local thrombosis when the blood is rendered noncoagulable.[18, 19] The former hazard of immediately recurring thrombosis that necessitates reopening of the vessel has been largely averted by either systemic heparinization in the preoperative period or local irrigation of the arterial lumen at the time of surgery.[8, 21] In the same manner, heparin does much to deter the formation of a distally propagating thrombus. There is some evidence to indicate that it may actually resolve early thrombi.[14]

In the cases reported to date, local heparin therapy has been used only for irrigation of the opened vessel at the time of repair.[1, 8, 9] Chief reliance is placed upon the systemic administration of heparin, either as a continuous intravenous flow or by intermittent injection at regular intervals.

Feeling that a more direct method was indicated, Dr. N. E. Freeman originally proposed the idea of continuous intra-arterial injection of heparin through an inlying needle proximal to the arteriotomy site. The use of flexible Polythene tubing, which can be sutured into place by the method indicated in Fig. 1 and allowed to remain during the postoperative period, makes this idea applicable to the surgery of peripheral emboli.

There would seem to be a definite advantage in a form of therapy which allows local arterial heparinization at the site of trauma and in the affected limb during and after the surgical procedure. If the anticoagulant effect can be confined to one limb, such therapy, in addition to guaranteeing an adequate supply of heparin at the point where it is needed, will avoid the inherent dangers of general heparinization.

Not the least of these hazards is hemorrhage. Murray[19] records two instances of fatal wound hemorrhage in dogs that were being given heparin to prevent

thrombosis. The heparin was administered in glass tubing used to bridge arterial defects. Troublesome bleeding from the operative wound has been our experience in working with heparinized animals. Three instances of massive wound hemorrhage, one of which was fatal, have been observed by one of us in patients receiving adequate systemic doses of heparin after embolectomy. Such a complication has been recorded by others.[13] It was of interest to note the absence of unusual bleeding during the course of the experiments here described.

Continuous intravenous heparin injection often requires the administration of large quantities of fluid each day. In this group of patients, who usually present cardiac problems, excessive fluid intake is dangerous. The deleterious effect of Dicumarol in patients with advanced hepatic or renal disease is well recognized. When it is appreciated that the high mortality rate in these patients is due not so much to the embolus or to the surgery as to the pre-existing disease, these factors assume more than minor importance. In the following case history, the extensive thrombosis added to the picture of severe systemic disease is representative of the problem so frequently encountered.

CASE REPORT

H. T., a 60-year-old white man, was first seen on Aug. 8, 1949, for a complaint of pain, coldness, anesthesia, and paralysis of the left leg of twenty-two hours' duration.

The first symptoms occurred at 3:00 A.M. of the preceding day, when he was awakened by pain and coldness of the left lower leg, extending to the knee. In the following four hours, the pain increased in severity and he noted paralysis of the foot and calf muscles and anesthesia below the knee. Twenty-one hours after the onset, he was seen by his physician, who referred him to one of us (E. J. W.) with a diagnosis of arterial embolus.

The past history indicated a coronary occlusion in 1944, chronic cardiac decompensation with auricular fibrillation, diabetes mellitus, and alcoholic cirrhosis of the liver.

Examination showed an acutely ill elderly man complaining of severe pain in the left lower leg. Blood pressure in the left arm was 120/70. Slight distention of the cervical veins was noted. The heart was enlarged, extending 11 cm. to the left of the mid-sternal line. The cardiac rhythm was grossly irregular at a rate of 92. There was a radial pulse deficit of 12. The liver was palpable 9 cm. below the costal margin. The left lower leg showed pallor and anesthesia to a level 5 cm. above the knee. There was complete motor paralysis of the calf and foot muscles. Arterial pulsation could be obtained as far distally as the common femoral artery. No circulatory abnormalities were observed in the right leg. With a diagnosis of embolic obstruction of the left common femoral artery, the patient was taken to the operating room for embolectomy.

Under nitrous oxide-ether anesthesia, the left femoral artery was surgically exposed. The embolus was found to occupy the common femoral artery at its bifurcation. The superficial femoral artery distal to it was occluded by a firm thrombus. After extension of the incision and division of the fascia of the adductor muscles, the thrombus was found to extend beyond the bifurcation of the popliteal artery. The femoral artery was occluded with rubber tubing, and the embolus removed by arteriotomy at the bifurcation of the common femoral artery, thereby clearing the lumen to a point beyond the origin of the uninvolved profunda femoris. After closure of this incision, the clamps were removed and a segment of Polythene tubing was introduced into the common femoral artery at the level of the inguinal ligament and passed proximally in the vessel for 6 cm. The internal diameter of the Polythene tubing was 0.010 inch. A previously placed purse-string suture was drawn up to secure the tubing. A No. 27 hypodermic needle was inserted into the opposite end of the tubing and connected to a flask containing heparin in 5 per cent glucose in water at a concentration of 10 mg. per

100 c.c. This solution was continuously infused into the artery throughout the remainder of the procedure at a rate of 30 drops per minute. Through a second incision in the superficial femoral artery, the distal thrombus was removed over a 12 cm. distance. Through a third incision in the superficial femoral artery at the lower end of Hunter's canal, the distal fragment of the thrombus, measuring 40 cm., was gently extracted from the popliteal and tibial vessels (Fig. 4). Free arterial backflow from the popliteal artery occurred at this stage. After closure of this incision, strong pulsations could be palpated in the popliteal artery. The coagulation time of the blood in the femoral artery at this time was fifteen minutes. No unusual bleeding was evident in the wound. After closure of the incision around the Polythene tube, which was left in place, the patient was returned to his room in good condition.

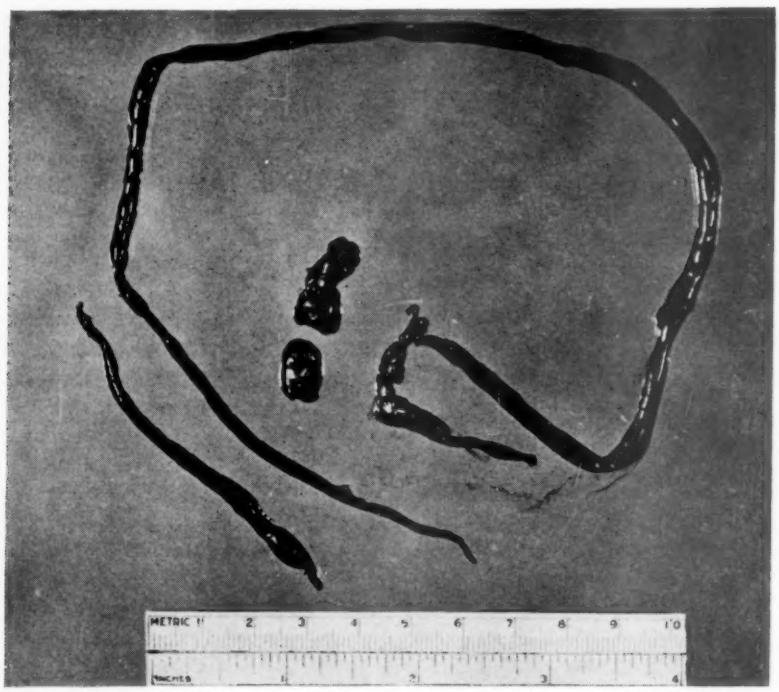

Fig. 4.—Photograph of the embolus and distal thrombus removed at surgery.

Within the following hour, the color and temperature of the left foot became normal and the posterior tibial pulsation could be felt. Arterial blood, abnormal only in its clotting power, could readily be obtained from the toes for coagulation time determinations. By raising the reservoir bottle to seven feet above the patient, the heparin infusion rate could be kept constant at 15 drops per minute. It was necessary to increase the concentration of heparin to 30 mg. per 100 c.c. to maintain the coagulation time at fifteen minutes. At this rate and concentration, there was no noticeable effect on the coagulation time of blood taken from the antecubital vein.

Six hours after surgery, the patient suddenly developed the clinical picture of shock. Except for the left leg, which remained warm, his skin became cold and moist. The blood pressure fell from 120/70 to 70/30 and anuria developed. The venous pressure rose from 15 cm. to 29 cm. of water over an eight-hour period; however, the lung fields remained clear. Despite supportive therapy, the course was progressively downhill, and twenty-four hours after operation the patient expired. An autopsy was not obtained.

COMMENT

Despite the fatal outcome in this case, the fact that the circulation was re-established and maintained in a limb with extensive and prolonged vascular damage has supported our conviction that continuous regional heparinization is desirable.

In this instance, we were able to obtain Polythene tubing of finer caliber than was used in the animal experiments. It was anticipated that it could be removed without danger of bleeding after the heparin was discontinued. The tubing was introduced into the artery in a proximal direction to increase the likelihood of rendering the entire stream of blood noncoagulable as it reached the first site of intimal damage. The ease with which the tubing could be passed suggested that it could be advanced from the femoral artery to a point above the aortic bifurcation for use in cases of saddle embolus.

Although experimental data from the use of heparin to protect arteriotomy wounds from thrombosis indicate that heparinization should be maintained for at least seventy-two hours,[13] further experience is required to determine the period of maximum benefit of regional heparinization in such patients.

SUMMARY

1. A method for the continuous intra-arterial injection of heparin is described.

2. Experimental data is presented, demonstrating that such a method can satisfactorily produce regional heparinization without influencing the clotting mechanism of the systemic blood.

3. The therapeutic implications are discussed and illustrated by a clinical case.

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SAPHENOUS NEURECTOMY IN THE TREATMENT OF SELECTED CASES OF PAINFUL ULCERATION OF THE LEG

LAWRENCE N. ATLAS, M.D., CLEVELAND, OHIO

(From the Departments of Surgery and Anatomy, School of Medicine, Western Reserve University)

AS A sequela of phlebitis and venous stasis of the leg, an ulcer with the following distinguishing features may develop.

Subjective Characteristics.—The lesion is excruciatingly painful. The pain is disabling. It is definitely causalgic in nature. The pain is described as burning or throbbing, and is worse at night. The pain is aggravated by recumbency; it is difficult for these individuals to remain in bed with the leg elevated, which accounts, in part, for the indolence of the lesion. Emotional disturbances aggravate the pain. These patients are invariably nervous and apprehensive.

Physical Characteristics.—The ulcer is situated in the medial aspect of the lower third of the leg just proximal to the internal malleolus. The ulcer is indolent and frequently infected. Surrounding it is a zone of inflamed causalgic-like skin. The ulcer and adjacent tissues are exquisitely sensitive to any type of manipulation or stimulation. Local pressure from an elastic bandage or stocking is unbearable. Only the blandest ointments are tolerated. A band of sensitive indurated tissue can be frequently palpated along the inner aspect of the leg between the ulcer and the knee. A constant diagnostic finding has been a spot of exquisite tenderness to deep pressure directly over the point where the saphenous nerve pierces the deep fascia of the leg. This point is located at the medial border of the tibia where it merges with the flare of the internal tibial condyle of the knee joint. These various objective findings are illustrated in Figs. 1 and 2.

Comment.—The peculiar subjective and objective features suggest that inflammatory irritation of a regional sensory nerve is responsible for the causalgic character of the lesion, and that resection of this nerve might relieve the intractable pain. On the basis of the location of the lesion and the regional sensory nerve anatomy, the saphenous nerve is considered to be the one requiring resection.

ANATOMY OF THE SAPHENOUS NERVE

The saphenous nerve, a branch of the femoral, is the longest cutaneous nerve in the body. It leaves the parent trunk shortly after the femoral enters the thigh, and pierces the lateral wall of the femoral sheath just distal to the bifurcation of the femoral artery. The nerve is intimately associated with the superficial femoral artery during its course through Scarpa's triangle and the adductor canal, first on the lateral and then on the anterior surface of the vessel; macroscopic sympathetic fibers from the saphenous nerve to the adjacent adventitia can be readily identified (see Fig. 2).

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Just proximal to the point where the femoral artery enters the popliteal space through the adductor hiatus, the saphenous nerve leaves the adductor canal and passes between the tendons of insertion of the sartorius and gracilis muscles. Beneath the deep fascia at the inner side of the knee joint, the nerve splits into many branches which pierce the deep fascia of the leg to become superficial, as indicated in Fig. 1. The terminal filaments of the saphenous

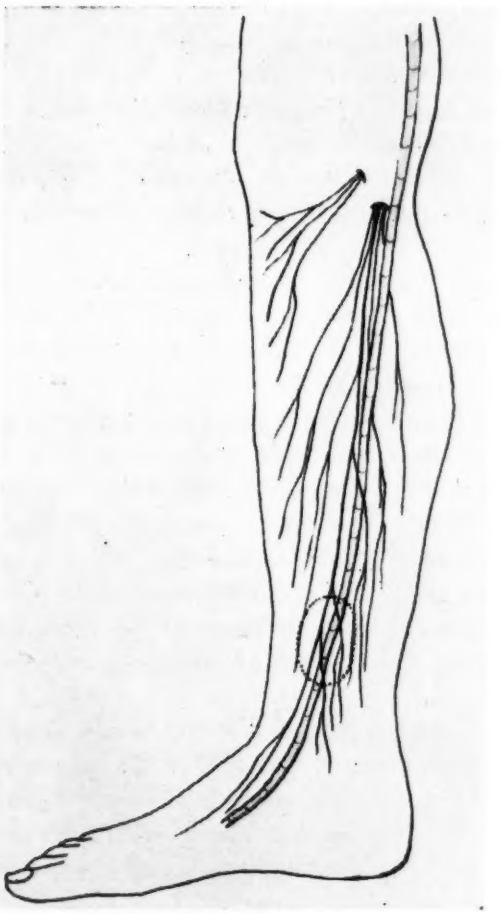


Fig. 1.

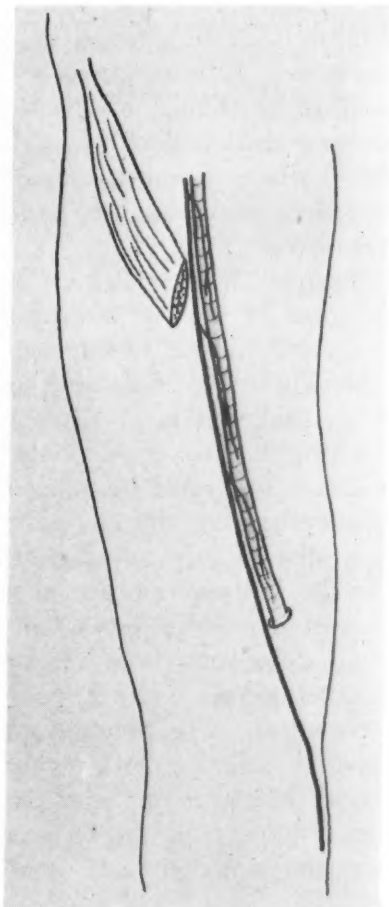


Fig. 2.

Fig. 1.—Diagrammatic sketch of distribution of terminal branches of the saphenous nerve. Dotted oval indicates location of ulcers which respond to saphenous neurectomy. Note point where nerve pierces deep fascia. Pressure here evokes severe pain, while pressure over saphenous vein just proximal to this point is painless.

Fig. 2.—Diagrammatic illustration of relationship between saphenous nerve and superficial femoral artery in the adductor canal. The major portion of sartorius muscle is removed. The saphenous nerve in the distal two-thirds of canal is displaced laterad to show the vasomotor fibers to arterial adventitia. The saphenous nerve carries both somatic sensory and sympathetic nerve fibers.

nerve innervate the sensory organs and blood vessels of the cutaneous and subcutaneous tissues of the medial aspect of the leg and foot. Some of these filaments may reach the great toe.

THE TECHNIQUE OF SAPHENOUS NEURECTOMY

It has been my observation that an adequate sensory and vasomotor denervation of the painful tissues can be obtained consistently only when the saphenous nerve is resected in the proximal portion of the femoral sheath. The operation is performed under regional infiltration anesthesia, which permits deliberate irritation and identification of the nerve selected for resection.

A vertical incision is made directly over the femoral artery from the base to the apex of Scarpa's triangle. Taking care not to injure the great saphenous vein, the incision is deepened to expose the deep fascia of the thigh, which is incised over the sartorius muscle. The latter is recognized by the direction of its fibers which run downward and inward. The muscle is mobilized and retracted outward to expose the subjacent femoral sheath. At this point of the operation, two cutaneous nerves are frequently seen. They are the intermediate and medial cutaneous nerves of the thigh, and should be preserved. The sheath is distended with procaine and opened for its entire exposed length directly over the pulsating superficial femoral artery. After the sheath has been opened, the saphenous nerve will be found within the sheath adjacent to the lateral surface of the artery. Directly posterior to the saphenous nerve is the motor nerve to the vastus medialis, which should not be disturbed.

The saphenous nerve is mobilized and gently squeezed with a hemostat. If the correct nerve has been obtained, the patient will complain of pain in the ulcer and inner leg. The proximal portion of the nerve is then injected with 2 per cent procaine and sectioned. The proximal end is crushed to control bleeding from the small artery accompanying it, but not ligated. Ligation of the nerve, particularly with nonabsorbable ligature material, increases the incidence of temporary postoperative paresthesia. The distal end of the cut nerve is displaced from the sheath and sutured into the fascia lata superficial to the replaced sartorius muscle. Regeneration of the nerve cannot occur.

A high saphenous vein ligation can be performed through the same incision. The terminal portion of the great saphenous vein and its tributaries can be readily located by opening the subcutaneous space medial to the upper portion of the incision.

CLINICAL RESULTS

During the past seven years a total of sixty-three saphenous neurectomies have been performed. Relief of pain and regional tenderness has been immediate and striking. At the completion of the operation, I frequently irritate the ulcer by débriding and cleansing it with ether with minimal reaction from the patient. Healing has also been expedited. Many of these previously indolent ulcers have healed within two to four weeks following surgery. The rapidity with which these ulcers have healed following saphenous neurectomy can be explained in two ways. The sensory denervation permits local medication and regional compression, and saphenous neurectomy constitutes a limited type of sympathectomy which improves the local blood supply. Approximately 50 per cent of patients undergoing saphenous neurectomy will experience paresthesia

in the denervated tissues. The paresthesia begins about one week following surgery and will persist for one month. I have seen no instance of permanent paresthesia, postoperative causalgia, or neuromas.

CASE REPORTS

In general, the patients operated upon can be placed in two groups: those in whom the ulcer occurred as a complication of deep venous inflammation with obstruction or insufficiency, and those in whom the ulcer complicated varicose veins. The former group comprised about two-thirds of the cases, the latter one-third.

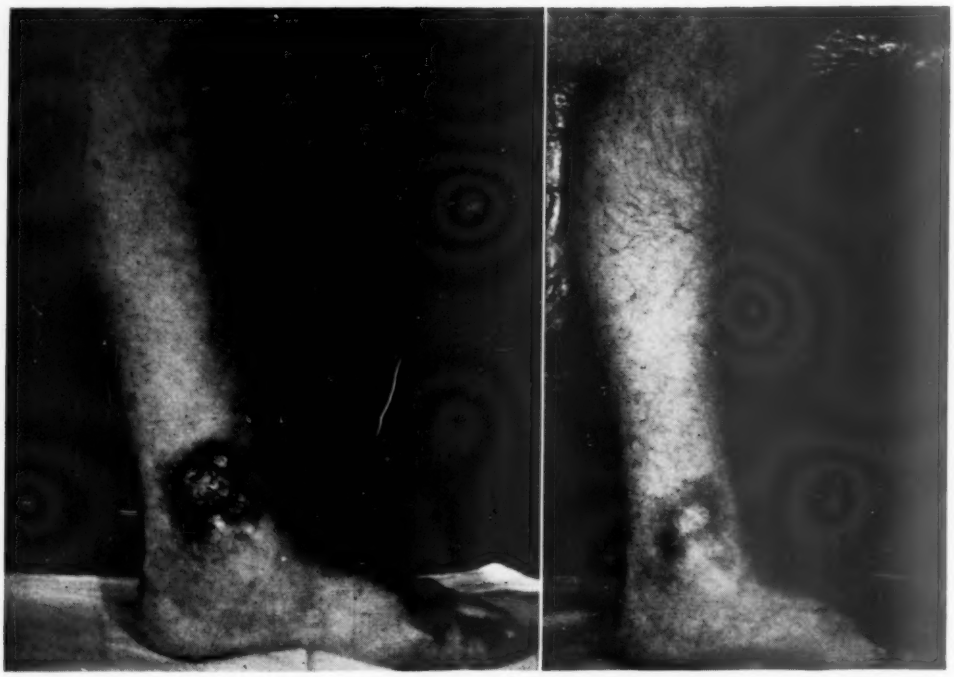


Fig. 3. Fig. 4.

Fig. 3 (Case 1).—Preoperative condition of ulcerated leg.

Fig. 4 (Case 1).—Photograph of ulcerated leg shown in Fig. 3, taken four weeks following saphenous neurectomy. Previously ulcerated tissue now healed and painless.

Individuals who have suffered an acute attack of iliofemoral thrombophlebitis with phlegmasia alba dolens not infrequently develop the peculiar type of ulceration amenable to saphenous neurectomy as a remote primary complication. Sometimes the ulcers appear as late as twenty-five years after the original vascular insult. The following case is representative of this group.

CASE 1.—A. L., a 50-year-old white woman, had a saphenous neurectomy which was performed September, 1943. There was a history of post-partum milk leg at the age of 25 years. For several years following the acute attack the leg swelled upon activity and was painful. Edema then disappeared, the limb became asymptomatic, and elastic support was discarded. The patient was well until the age of 45, when a sore spot which appeared on the leg developed into an ulcer. The ulcer healed with prolonged bed rest and local medication, but always recurred when the patient became ambulatory. Since the last re-

currence, the ulcer failed to heal and became unbearably painful. The ulcer throbbed and burned and the pain extended up the inner leg and thigh. The pain was aggravated by recumbency, emotional upsets, and aggravation.

The patient was extremely nervous and apprehensive and in obvious distress. There was an indolent infected ulcer in the medial surface of the lower third of the leg just proximal to the internal malleolus. The regional tissues were indurated and the skin was acutely inflamed (see Fig. 3). The ulcer was exquisitely sensitive to irritation. Extreme pain was provoked by pressure over the saphenous nerve in the upper leg. There were no varicose veins, no edema, and no arterial insufficiency. A phlebogram revealed a femoral vein which was ragged in outline and lacking normal valve structure. It was obviously recanalized and insufficient.

A sapheonus neurectomy was followed by immediate relief of pain and regional sensitivity. The patient was in the hospital for two weeks, during which time the ulcer was washed with ether every day and coated with zinc oxide ointment. Local medication was painless. At the end of two weeks an Unna boot was applied. When this was removed two weeks later, the ulcer was healed and has remained healed (see Fig. 4).

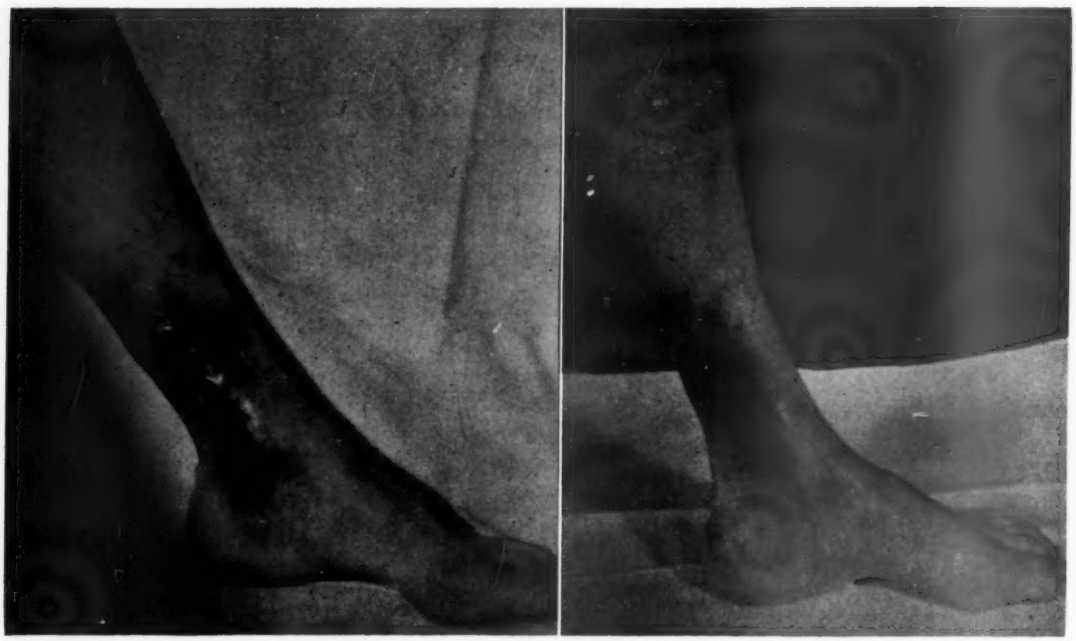
Included in this group of cases of postthrombotic ulceration were several which merit special consideration. They illustrate two important points: that every leg ulcer is not necessarily a "varicose" ulcer, and that it is the better part of wisdom to take seriously a history of an antecedent phlebitis or milk leg, always investigating the status of the deep venous circulation before utilizing peripheral vein surgery to cure a leg ulcer. While certain very carefully selected cases of the so-called postthrombotic syndrome may respond favorably to peripheral vein surgery, the injudicious use of saphenous and/or femoral vein ligation is not to be condoned.

CASE 2.—F. W., a white woman, 60 years of age, underwent saphenous neurectomy in July, 1947. At the age of 30 years, she had suffered a post-partum milk leg. She was confined to bed for several months with marked swelling of the leg, pain, and fever. The leg swelled upon activity following acute attack, but when varicose veins began to develop swelling decreased. Varicose veins continued to increase in size, and about five years previous to admission the patient developed an ulcer of the leg which healed and recurred repeatedly. Six months prior to consultation a high saphenous vein ligation was performed to "cure" the ulcer. Subsequently the ulcer enlarged and became extremely painful. The entire leg throbbed and burned, and the patient was unable to sleep because of the pain.

There was a large indolent infected ulcer of the left leg situated in the internal supramalleolar region. Varicose veins were present. The Trendelenburg test was doubly positive, and the Perthes test was positive and increased regional pain. The ulcer was surrounded by the usual causalgic-like skin. The ulcer itself was exquisitely sensitive, and severe pain was evoked by deep pressure over the saphenous nerve in the upper leg.

Saphenous neurectomy successfully desensitized the ulcer. Following operation, it was treated with continuous Dakin compresses until complete granulation permitted the application of a split-thickness graft. The ulcer has remained healed.

CASE 3.—J. B., a white woman, 34 years of age, underwent saphenous neurectomy in March, 1949. At the age of 29 years she had suffered a typical attack of acute post-partum iliofemoral thrombophlebitis with phlegmasia alba dolens. She was incapacitated for months, and when she resumed activity, the leg became swollen and painful. Three years later an ulcer appeared on the inside of the leg. Twelve months before I saw her, a high saphenous ligation had been performed despite the fact that, according to the patient, she had no varicose veins. Following surgery the ulcer became larger and more painful. Approximately six months previous to admission she underwent further surgery, which consisted of a ligation of the superficial femoral vein, a lumbar sympathectomy, and a skin graft. Within thirty



A. *B.*

Fig. 5 (Case ::).—*A*, Postthrombotic ulcer twelve months and six months after saphenous vein ligation and femoral vein ligation, respectively. Saphenous neurectomy relieved pain, but ulcer remained healed only when activity was curtailed. *B*, same leg as shown in *A*. After seven months of semi-invalidism and local treatment, the ulcer has healed and the patient has resumed full activity without recurrence. There has been no pain since saphenous neurectomy was performed.

Fig. 6. Fig. 7.

Fig 6 (Case 4).—Causalgic varicose ulcer just prior to combined saphenous neurectomy and proximal saphenous phlebectomy and resection of incompetent perforating vein of leg.

Fig. 7 (Case 4).—Same leg as shown in Fig. 6, three weeks following operation. Note the relatively fresh surgical scar of resection of incompetent perforating vein of leg and associated "blow-out" varix.

days after becoming ambulatory, the ulcer recurred and was attended by excruciating pain. The ulcer, leg, and inner thigh throbbed and burned constantly. The pain was worse at night, and, since she was unable to sleep, she resorted to narcotics. This patient was haggard from pain and lack of sleep, and was extremely nervous and apprehensive.

The condition of the leg is depicted in Fig. 5*A*. The ulcer and adjacent tissues were exquisitely sensitive, and severe pain could be produced by pressing over the course of the saphenous nerve in the leg. It should be noted that there were no varicose veins.

Saphenous neurectomy desensitized the ulcer and regional tissue. With local medication and elastic support, which were now comfortably tolerated, the ulcer healed. However, because of the serious impairment in venous drainage, the ulcer remains closed only if the patient's activity is sharply curtailed. It is to be hoped that with the development of collateral venous channels, healing will be permanent. To date, the relief of pain has been most gratifying.

True varicose ulcers, when favorably situated and unusually painful and indolent, respond favorably to the combined operation of saphenous neurectomy and proximal phlebectomy. In the case of varicose veins complicated by the causalgic type of ulcer described, neurectomy is considered to be an adjunct therapeutic measure utilized to secure immediate analgesia and rapid healing. The following case is typical of this group.

Case 4.—M. E., a white woman, 49 years of age, underwent a combined operation of saphenous neurectomy and proximal phlebectomy, which was performed February, 1944. The patient had had varicose veins since the age of 17. Six months prior to consultation a sore spot appeared on the leg which soon broke down to form an ulcer. Despite considerable local therapy, the ulcer increased in size and became very painful. The ulcer burned and the entire leg throbbed. The pain was worse at night, and recumbency increased the severity of the pain. The varices had never been treated. She wore an elastic stocking, but the regional tenderness had become so bad that the stocking could be no longer tolerated.

There was some edema of the ankle. A large infected ulcer was situated in the internal malleolar region of the right leg. The indolent ulcer was surrounded by a zone of inflamed causalgic-like skin (see Fig. 6). Local sensitivity was extreme; severe pain was evoked by pressure over the saphenous nerve in the upper leg. Large varicosities were present. The Ochsner segmental Trendelenburg test revealed valvular incompetency of the great saphenous vein at the fossa ovalis and an incompetent communicating vein in the upper leg. There was no evidence of deep venous pathology. The arterial circulation was normal.

A combined saphenous neurectomy and proximal phlebectomy was performed, plus a resection of the incompetent communicating vein. Local analgesia was secured, medication and pressure were tolerated, and one week following operation an Unna boot was applied. When the boot was removed two weeks later, the ulcer was healed (see Fig. 7). There has been no recurrence.

PERIANAL EXTRAMAMMARY PAGET'S DISEASE

Report of a Case

Wendell W. Green, M.D., and Francis W. Epstein, M.D., Toledo, Ohio

(From the Department of Surgery, St. Vincent's Hospital)

SIR James Paget,[1] in his original description of the disease which bears his name today, mentioned one case of dermatitis involving the penis. He interpreted this lesion on the penis as an extramammary Paget's disease, and since his original paper the subject has been under considerable controversial study. The problem of which comes first, the "eczema" of the skin or the underlying or adjacent carcinoma, remains in dispute. When extramammary Paget's disease occurs and no underlying carcinoma evidences itself the problem becomes more complex, because then the question arises as to the origin of the Paget cells. Radcliffe Crocker,[2] in his paper of 1889, first suggested that they develop from sweat glands. Pinkus and Gould,[5] in a much later paper, reporting their case of extramammary Paget's disease suggested that the Paget cells may be associated with an underlying rectal malignancy.

A review of the literature reveals only four cases that have been accepted as extramammary perianal Paget's disease. Weiner[3] cited two cases, those presented by Darier and Couillaud, in which no carcinoma was found, and that of Arzt and Kren, in which a rectal carcinoma was present. Eberts[4] described an adenocarcinoma primary in the apocrine glands, stating that it was "an example of the extramammary Paget lesion, developing in this instance in the epidermis of the margin, secondary to the primary carcinoma of the vestigial anal scent glands." Pinkus and Gould reported a case of their own associated with a rectal carcinoma, and in the same paper accepted the cases of Arzt and Kren and of Eberts as examples of extramammary Paget's disease of the perianal area.

The presence of a rectal carcinoma in the cases of Pinkus and Gould and of Arzt and Kren prompted the former to emphasize the analogy between the lesion on the nipple associated with an underlying mammary carcinoma and the perianal disease in the presence of a rectal carcinoma. This analogy was pointed out in a written comment which accompanied Pinkus' report on the biopsy specimen from the case reported here. The absence of any carcinoma under rectal or sigmoidoscopic examination in our case refutes the interesting suggestion that a rectal carcinoma might be found in all cases of proved perianal extramammary Paget's disease. Most of the cases of extramammary Paget's disease reported in the literature have been found in areas profusely supplied with apocrine glands, and it is quite possible that the tumor in our case originated in one of the sweat glands of the perianal area.

CASE REPORT

A. R., a 65-year-old widower, a white man, consulted us Sept. 25, 1946, because of localized perianal itching of seven years' duration. Examination revealed a sharply circumscribed ovoid lesion measuring 4 by 6 cm. involving the right perianal area. The medial

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border impinged upon the right anal margin, but the bulk of the tumor involved the skin. Several irregular superficial ulcers, none measuring more than 3 or 4 mm. in size, were present on the surface, with intervening islands of white tissue superimposed over the entire erythematous base (Fig. 1). The remaining perianal tissue had a normal appearance. Nothing of significance was found on anoscopic examination except moderate-sized but symptomless internal hemorrhoids. The sigmoidoscope was passed up to a point 25 cm. from the anal margin and no pathology was found above the canal.

The patient was seen in consultation (by F. W. E.) and a biopsy specimen was removed under local anesthesia. The pathologic examination was made by Dr. Hermann Pinkus of Monroe, Mich., who reported that the sections from this patient showed a true picture of extramammary Paget's disease.

Histologic findings by Pinkus were as follows: The epidermis showed moderate and rather even thickening. It had a multiple granular layer and thick hyperkeratosis, with minimal parakeratosis. The basal layer, rete, and horny layer contained many afibrillar cells which in the higher strata resembled corps ronds and grains. In the lower strata there were round elements about the size of prickle cells with fairly darkly staining oval nuclei, some of which were in mitosis. Some of the cells in the basal layer were arranged in rosette

Fig. 1.—Preoperative appearance of patient with perianal extramammary Paget's disease.

form, suggesting glandular formation. The upper corium contained clumps of dense lymphocytic and plasmocytic infiltration, but nowhere were any tumor cells present in the corium, except where they followed the follicular epithelium downward. Staining with mucicarmine revealed mucin in a considerable percentage of the afibrillar cells (Fig. 2). The diagnosis was extramammary Paget's disease.

The patient refused any surgical procedure at that time, but on April 22, 1947, operation was performed by one of us (W. W. G.) at St. Vincent's Hospital. The entire lesion was extirpated by the cutting current; except at the medial border, the incision was made about 1 cm. beyond the edges of the tumor. In order to avoid postoperative stenosis at the anal margin the incision was kept close to the border and carried down to the sphincter. Healing progressed satisfactorily and the entire area was covered with healthy skin on June 23, 1947. At that time there was no evidence of recurrence at the anal margin and there was no stenosis of the orifice (Fig. 3).

The pathologic findings of Dr. T. E. Ramsey, pathologist at St. Vincent's Hospital, corroborated the diagnosis of extramammary Paget's disease made previously by Dr. Pinkus; neither he nor Dr. Ramsey found any evidence of an invasive carcinoma in the larger specimen.

The patient returned Jan. 28, 1948, for a routine checkup, stating that a mild but persistent itching had been present in the anterior anal canal for the previous two or three months. The lower anterior canal was involved by a small lesion similar in appearance to the original one; the sigmoidoscopic examination was again negative. This recurrence was apparently due to extension resulting from inadequate removal of tissue in the desire to

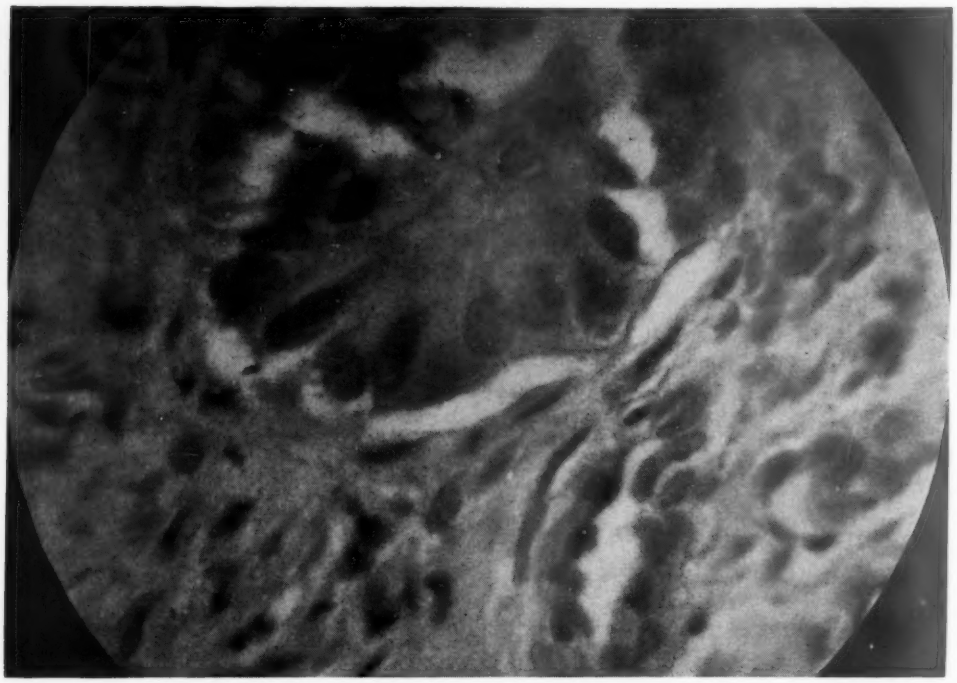

Fig. 2.—Group of high columnar cells forming an "acinus" at the derma-epidermal border.

Fig. 3.—Postoperative appearance (11 weeks after surgery).

insure a good functional result. The patient would not consent to an additional operative procedure because of the mildness of the symptoms and his fear of the possibility of impairment of sphincter action.

A still later follow-up on April 21, 1948, demonstrated a further extension of the process with a recurrence within the healed scar of the skin. The patient has refused further therapy, either surgical or x-ray.

SUMMARY

A case of extramammary Paget's disease of the perianal skin is presented, in which there is no evidence of associated carcinoma in the rectum or sigmoid up to a point 25 cm. from the anal margin.

The importance of biopsy in unusual lesions of this type is demonstrated; the tumor cited here had been diagnosed as a neurodermatitis by several physicians and in two prominent medical centers over a period of seven years.

The recurrence of the lesion seven or eight months after operation emphasizes the fallacy of sacrificing wide dissection at all points in the interest of conservation of function.

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RUPTURE OF THE BOWEL IN THE NEWBORN INFANT

Including a Case Report of Rupture in the Large Intestine With Recovery

C. Marshall Lee, Jr., M.D., and Bruce G. MacMillan, M.D.,
Cincinnati, Ohio

(From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Surgical Services of the Children's Hospital and the Cincinnati General Hospital)

RUPTURE of a hollow viscus in a newborn infant is an unusual occurrence and is accompanied by an extremely high mortality. A considerable number of cases have been reported in the literature, but nearly all writers agree that the incidence is higher than is generally supposed, since a significant number of newborn deaths are attributed, without autopsy or operation, to other causes. Prompt recognition and aggressive surgical treatment can save many of these infants. Although Selinger[32] records recovery in a three-month-old infant with walled-off perforation of a gastric ulcer, we have been able to find only one previously reported recovery from rupture of the bowel in a newborn infant. This patient had a spontaneous rupture of the terminal ileum and recovered following simple closure of the perforation. The report presented herewith concerns the first newborn infant, as far as we are able to determine, to recover from rupture of the large bowel with or without associated congenital anomaly.

The most thorough and comprehensive reviews of the subject are those of Abt,[1] in 1931, and Thelander,[36] in 1939. The literature from this time until 1943 has been ably reviewed by Agerty, Ziserman, and Shollenberger[3] in reporting their one case of a patient who recovered. The present discussion does not propose to present a complete review of the subject, since the writers mentioned have so recently presented their contributions. This paper, therefore, will summarize certain aspects of the problem with the hope that it will contribute toward lowering the extremely high mortality of this condition. It is essential to review the etiological possibilities because effective surgical treatment depends primarily on a clear understanding of the underlying causes of the perforation.

Although in this report we are primarily concerned with rupture of the small and large bowel, it should be mentioned that perforation of gastric and duodenal ulcers in newborn infants has been reported many times since Siebold's case in 1825.[33] Thelander assembled forty-six cases from the literature, and this abdominal emergency in the newborn infant occurs with sufficient frequency to be discussed in most standard texts of pediatrics and pediatric surgery. The cause is as obscure in infants as it is in adults, but the treatment is obvious. Prompt recognition and immediate surgical closure are, of course, essential. The site of perforation may be difficult to determine before operation, and the clinical findings, except in free perforation with pneumoperitoneum demonstrable roentgenologically, may be difficult to evaluate. However, alertness to the possibility of the disease, together with modern surgical and sup-

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portive techniques and the use of antibiotics, should make it possible to save an increasing number of these patients.

Perforation of the small or large bowel in newborn infants may result from a variety of causes. Since proper management of a perforation from one cause may be quite different from that of a similar perforation from another cause, it is here that the aphorism "forewarned is forearmed" becomes of especially great importance. In seeking possible causes for rupture of the bowel in newborn infants, the natural assumption is that obstetrical trauma would play a prominent part. Titus[37] commented in this connection as follows: "Injuries to the infant's abdominal viscera can be caused by roughly grasping the child's abdomen and making traction over this soft unprotected wall during a breech extraction. Various viscera may be involved, including liver, spleen, kidneys, and intestines." However, the sections on birth injuries of the newborn infant in several other obstetrical texts make no mention of injury to the intestines, and Thelander discounts it as a contributing factor.

Russell[31] collected thirty-nine cases of bowel rupture in newborn infants, some of which had been included in Thelander's report. Of these thirty-nine cases, there were twenty-eight which Russell believed might have been indirectly due to obstetrical trauma, but because they are not recorded and analyzed in detail evaluation is not possible. Examination of the reports of those cases for which references are given leaves considerable doubt as to whether obstetrical trauma played a part. Zillner,[39] in 1884, reported four cases of rupture of the sigmoid colon which he attributed to obstetrical trauma. However, one of these infants was delivered spontaneously after an easy labor and all four infants had been given enemas by midwives shortly after birth. All four were vertex presentations. The perforations were respectively 18.5 cm., 17.0 cm., 26.5 cm., and 15 cm. from the anus. Zillner conducted experiments, which Russell quoted in support of his view, to show that it is difficult to rupture the bowel by an enema given roughly or under too much pressure. Russell offered the alternative suggestion that, "It is evident that the rupture which occurs during birth is due to hydrostatic pressure within the bowel, caused by pressure of the birth canal acting on a collection of meconium which cannot pass along the intestinal lumen due to being caught in an angulation or pouch." Rupture of the bowel by hydrostatic pressure from an enema is just as probable as perforation by hydrostatic pressure from meconium. Since all of the infants Zillner mentioned had received enemas administered by unskilled midwives, and all showed perforations a short distance from the anus, obstetrical trauma appears the less likely possibility. Since the bowel contains no gas until after birth, except in exceptional circumstances, it is difficult to imagine that the normal, undistended bowel could be ruptured by pressure either of the obstetrician's hands or of the birth canal. No conclusive case of rupture of the normal bowel due to obstetrical trauma alone has been found. It cannot be said that such an accident is impossible, but it would appear to be highly improbable. Hence, even in the presence of a history of obstetrical trauma, if pre-existing congenital anomaly is sought, it will usually be found.

Nevertheless, the occurrence of "spontaneous" or unexplained rupture of the bowel in newborn infants is well recognized and adequately documented. Thelander collected thirty-nine cases in which trauma and associated obstructing anomalies were carefully excluded, although she did include Zillner's four cases. The causes of such perforations are usually obscure, and, though various possibilities have been suggested, there is no consistent incidence of any one of them. Blood stream infections in the mother, maternal contamination of amniotic fluid, infection of the cord stump with positive blood culture of the infant, false diverticula of the bowel wall, and erosion of ulcers with or without Meckel's diverticulum have been mentioned.[7, 14, 19, 27] Suffice it to say that rupture of the bowel can occur in the absence of obstruction, and if the latter has been excluded by careful search, simple closure of the perforation is all that is necessary. The case with recovery reported by Agerty and his associates was of this type. Although rupture of the bowel may occur in newborn infants in the absence of obstruction, this is the exception rather than the general rule, and, as our case illustrates, the assumption that simple closure of a perforation is adequate when the bowel is not proved to be patent throughout can lead to disaster.

The two most common causes of obstruction leading to perforation are atresia and meconium ileus, and unless a differential diagnosis can be arrived at preoperatively the surgeon should be prepared for either situation, since the surgical management differs markedly.

Congenital atresia of the bowel represents a complete obstruction of the alimentary tract either by a diaphragm of intrinsic bowel tissue or by complete absence of a segment of bowel with only a stringlike residuum without a lumen. The condition and its management were ably discussed by Ladd and Gross[24] and by Potts.[30]

The obstruction derives from a failure of recanalization of the bowel after it goes through a solid phase of development during the fifth to tenth weeks of fetal life. Such complete obstructions are most common in the small bowel, but a few cases in the colon have been encountered. Ladd and Gross mentioned four atresias of the colon in a series of fifty-two cases. Potts reported the first case of atresia of the transverse colon with recovery. There was no perforation in this case. Steindl[34] of Vienna reported a case of rupture of the hepatic flexure in a 60-hour-old male infant, which he attributed to a "contraction ring," but with a careful reading, his report suggests that the infant probably had a true congenital atresia in the transverse colon. Ficarra and Degen[18] reported a rupture of the ileum proximal to an atresia three and one-half inches above the ileocecal valve. A number of cases with multiple atresias have been reported.

As Ladd and Gross pointed out, the rapidly increasing distention above the point of atresia leads to ischemia of the gut and finally to sufficient localized ischemic necrosis for rupture to occur. Such ischemic necrosis is by no means comparable to the gangrene of volvulus or intussusception. Once the bowel ruptures and deflates, the blood supply may improve and the margins of the

perforation may appear perfectly clean except under the closest scrutiny. Therefore, the appearance of the torn bowel may give no clue to the presence of a more distal obstruction.

Further, the presence of a perforation strongly suggests that obstruction is complete. Perforation is seldom if ever seen in stenosis of the bowel. This congenital stricture derives from the same anomalous mechanism as does atresia, but partial recanalization has occurred so that the obstruction is incomplete. Since a "safety valve" exists for the distribution of gas to the bowel distal to the stricture, distention is not so violent or rapid in development and is less sharply localized and rupture is less likely. Ladd and Gross stated that they have never encountered rupture of the bowel in cases of stenosis. Such stenoses are not necessarily incompatible with life and may not be discovered until long after the neonatal period. Therefore, in the large majority of cases when rupture of the bowel occurs in newborn infants, a complete obstruction distal to the site of perforation can be found.

Another cause of complete obstruction and associated rupture of the bowel is the condition known as "meconium ileus." The first recognition of this entity and its relation to fibrocystic disease of the pancreas was published by Landsteiner[25] in 1905, but its importance was not generally appreciated until Anderson's[4, 5, 6] and Farber's[16, 17] studies clarified the status of both meconium ileus and the so-called "celiac syndrome." Farber carefully studied eighty-seven cases of fibrocystic disease of the pancreas and concluded that the disorder represents a systemic disease affecting variously and in varying degrees the secretory cells and ducts of the pancreas, the salivary glands, the liver, and the tracheal and bronchial glands. When the pancreas is primarily or predominantly involved, the impaired secretion of pancreatic enzymes results in improper digestion of meconium. This produces meconium which is so thick and sticky that it behaves almost like partly dried glue and will not pass through the intestinal tract, becoming firmly impacted and producing complete obstruction, usually in the ileum. Farber has suggested that when the pancreas becomes affected ". . . during the latter part of intrauterine life, physically altered meconium will result which will cause intestinal obstruction shortly after birth." If the pancreatic disease does not appear until after the neonatal period, when bowel function has been established, ". . . the disease picture will be that of the celiac syndrome." Rupture of the bowel above the level of obstruction due to meconium ileus has been reported a number of times,[23, 29] though it apparently does not occur as commonly as with atresia of the bowel.

It is apparent that other causes of rupture of the bowel are possible, either alone or in conjunction with one of the above factors. It is recognized that volvulus is a frequent complication of meconium ileus or of atresia, and when it occurs it must be corrected surgically. In general, however, the perforation of a gangrenous bowel resulting from volvulus or intussusception is only incidental to the dominant pathology and need not be dealt with in the present discussion. Similarly, obstructions of the bowel due to constricting congenital bands, often associated with malrotation of the bowel, may play a part, but, as

in stenosis of the bowel, obstruction in such situations is usually incomplete and rupture of the gut is extremely rare if it occurs at all.

The clinical picture of perforation of the bowel in the newborn infant is quite characteristic. It has been described by Thelander as follows: "An infant with perforation peritonitis present at birth or occurring soon after presents a fairly classic picture. The little patient looks sick. He is cyanotic, the respirations are rapid and grunting, the abdomen is distended, and the abdominal wall, the flanks and the scrotum or vulva are usually edematous. Frequently brawny induration of the edematous area, which may resemble erysipelas, is also present. Food is taken poorly or not at all. Vomiting is frequent and persistent. The vomitus contains bile and may contain blood. The stools are either absent or scant. Some mucous or blood may be passed. [It should be remembered that Dr. Thelander's cases were all perforations in the absence of obstruction.] The temperature may be subnormal, but varying degrees of fever have been reported. The blood count is of little or no value. The hemoglobin content may be very high which probably indicates only dehydration. The leukocytes may or may not respond with a rise. . . . In cases of intrauterine perforation, the abdomen has at times been so distended at birth that delivery was impossible until paracentesis of the abdomen had been performed."

Thelander made no mention of roentgenologic findings. The appearance of a flat film of the abdomen is quite characteristic, with a massive pneumoperitoneum and diffuse distention of the bowel. This is usually sufficient for the diagnosis of ruptured bowel, and certainly in the presence of perforation, barium contrast studies are contraindicated and should not be employed. Barium enema may be very helpful in cases of suspected atresia, meconium ileus, and so on, without perforation, since the tiny undistended colon is virtually diagnostic of complete obstruction higher up, whether or not the barium can be made to reach the point of obstruction.[36] A diagnosis of "microcolon" might erroneously be made from the appearance of this tiny undistended bowel. Upper gastrointestinal series is less helpful and certainly dangerous and should be avoided in all but very exceptional cases. As Cohen,[12] Swenson and Ladd,[35] and Neuhauser[28] have pointed out, the danger of aspiration of barium in an infant who is vomiting is very great, and usually plain films of the abdomen and thorax will provide adequate information. Contrast media may occasionally be needed in esophageal atresia or diaphragmatic hernia, and when this is necessary Lipiodol is much safer than barium. We believe that neither barium nor Lipiodol should be used in the presence of known or suspected perforation. Moreover, rupture is most unlikely in obstructions above the pylorus, and when the obstruction is below this point, the distention and regurgitant motion of the bowel may make it difficult, if not impossible, to demonstrate the exact site of obstruction. Even though no contrast study is done, continuous gastric suction is an important part of the pre- and postoperative care, and, from a diagnostic standpoint, the successful passage of the tube into the stomach (roentgenologically confirmed) is valuable in ruling out atresia of the esophagus if bile-stained vomitus has not been observed at first hand. Multiple atresia involving

both the esophagus and the bowel has been reported a number of times, although in such circumstances one would not expect distention of the gut to produce rupture before atresia of the esophagus was discovered.

A patient recently under our care illustrates several important points in the diagnosis and management of this condition. We have endeavored to record this case in the light of our reasoning at the time and in the following discussion to point out certain revisions of procedure which we believe will improve the management of similar cases in the future.

CASE REPORT

V. M., a 2½-day-old white male infant weighing 8 pounds 4 ounces, was referred to the Children's Hospital on April 27, 1949, because of persistent vomiting and severe abdominal distention. The child had been delivered in another hospital and for the first eight to twelve hours of life had shown no evidence of disease. It was learned directly from the obstetrician who had attended the mother that the delivery had been difficult and somewhat traumatic, involving forceps extraction of a vertex presentation. After the first eight hours the child began to regurgitate water and formula, and thereafter violent and repeated vomiting developed simultaneously with rapidly increasing abdominal distention. The vomitus was at first bile-stained and then became "fecal" (meconium) in character. There was, however, a definite history of the passage of "normal meconium stools" confirmed by the record of five such stools in the nursing notes made at the referring hospital.

On admission the infant showed moderately severe dehydration. The temperature was 100.6° F. (rectal), and in addition to the signs of dehydration and hyponatremia, the physical examination was not remarkable except for a gross and very marked distention and tympany of the entire abdomen. The chest was clear except for elevation of the diaphragm incident to the abdominal distention. There was a brawny pitting edema of the lower abdominal wall, most pronounced in the right lower quadrant but later spreading across the entire suprapubic region. This led some of the earlier observers to suspect the presence of an intra-abdominal mass in the right lower quadrant. There was no increased local heat, and discoloration was difficult to evaluate since Merthiolate had been applied quite liberally to the umbilical stump and was distributed all over the abdomen. There was no gross evidence of infection of the stump.

Rectal examination had been made by a pediatrician prior to surgical consultation. This revealed a small but otherwise normal rectal ampulla, but when a nasal speculum was introduced by the same examiner, about 4 to 6 c.c. of seromucous fluid was released. A stained smear of this material showed a few polymorphonuclear leucocytes and scattered bacteria, and in view of the history of "normal meconium stools" the examiner mistook this so-called "white meconium" for pus, which he believed he might have drained inadvertently in introducing the speculum. This, coupled with the suspected presence of an intra-abdominal mass, led the earlier examiners to suspect an intra-abdominal abscess

TABLE I

ADMISSION DATE	4/27	4/28	4/29	4/30	5/2
R.B.C. (millions)	5.01	4.08		4.44	
Hb. (Gm.)	19.8	16.1	16.4	15.1	14.3
W.B.C.	16,900	11,550			13,950
N.P.N. (mg. %)	50	45	46	38	24
pH	7.49	7.48	7.51	7.44	7.39
CO_2 (mM./L.)	28.8	23.6	19.8	23.5	28.2
CO_2T (mm. Hg)	38	32	25	34	47
Cl (meq./L.)	101.2	89.2	94.4	98.4	104.8
Serum protein (+Gm. %)		4.6		3.8	4.1

Fig. 1.—Horizontal and vertical anteroposterior films and a vertical lateral projection of the abdomen on admission showing extensive pneumoperitoneum and diffuse bowel distention. Fluid levels both within the bowel and outside of it are plainly seen.

of undetermined origin. Later examiners were unable to demonstrate any intra-abdominal mass, and the diagnosis of ruptured hollow viscus became apparent when three-dimensional films were taken (Fig. 1). These showed a massive pneumoperitoneum and many dilated loops of bowel among which a differentiation between large and small bowel was virtually impossible. Both intraluminal and extraluminal fluid levels could be demonstrated. Laboratory studies are listed in Table I.

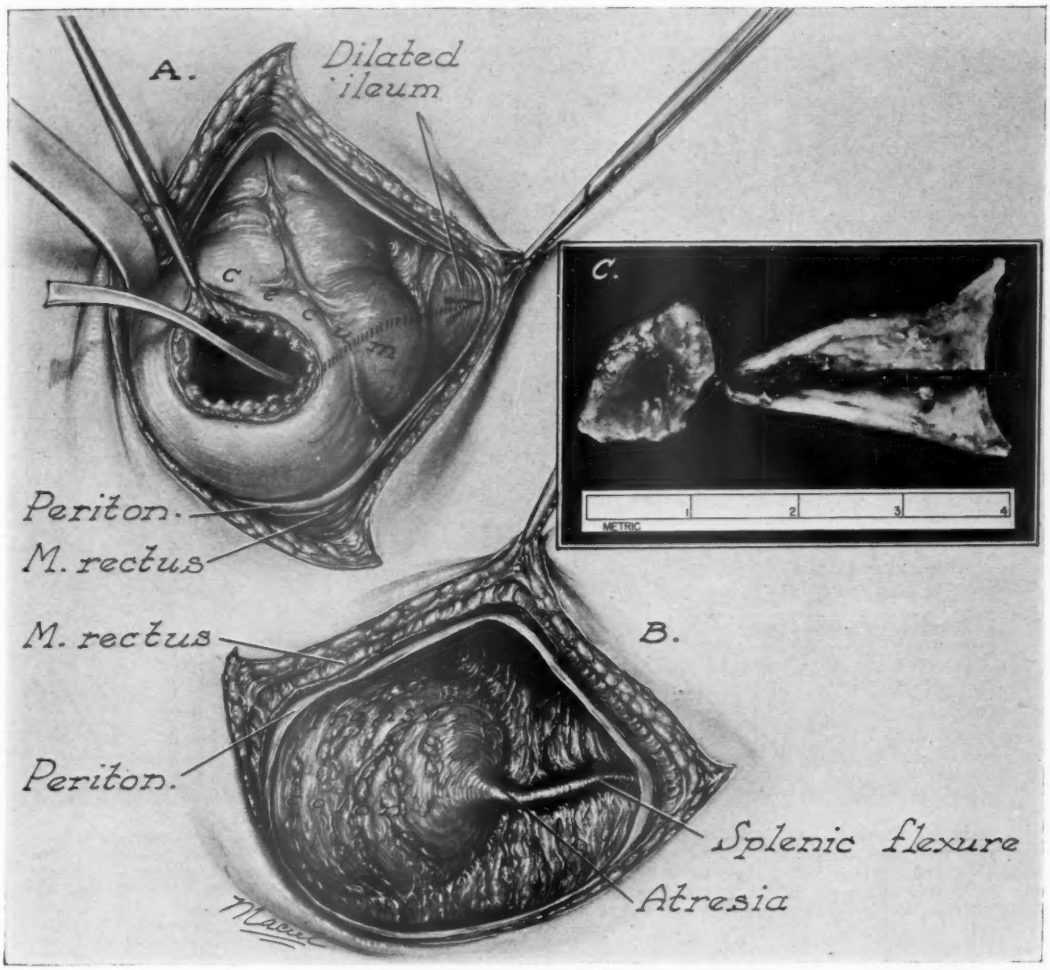

Fig. 2.—Artist's drawing showing *A*, the appearance and location of the large perforation of the cecum and *B*, the appearance of the atresia of the transverse colon, with the hugely distended colon proximal to the obstruction and the small collapsed bowel distal to it. Insert *C* shows the specimen removed at the first resection. The atresia was complete and would not admit a probe.

It was apparent that there was a ruptured hollow viscus and, although the need for surgical intervention was obvious, the choice of procedure devolved fundamentally on the cause of the perforation. The possibility of atresia was entertained, but because of the reliable history of traumatic delivery (under the impression that traumatic perforation was a tenable diagnosis) and the apparently reliable history of the passage of five normal meconium stools, it was concluded that perforation without obstruction was present. In the presence of known perforation we were reluctant to attempt confirmation by barium enema.

Accordingly, a gastric suction tube was introduced and immediate steps were taken to restore fluid and electrolyte balance. After five hours the patient's condition seemed satisfactory for operation.

Exploration was performed under local anesthesia through a small right rectus incision in the para-umbilical region, later extended a short distance caudad. When the peritoneum was opened there was a puff of escaping gas which had no appreciable odor, and profuse drainage of a large quantity of dark greenish-black meconium of normal consistency. Culture of this was later reported to show hemolytic *Staphylococcus aureus*.

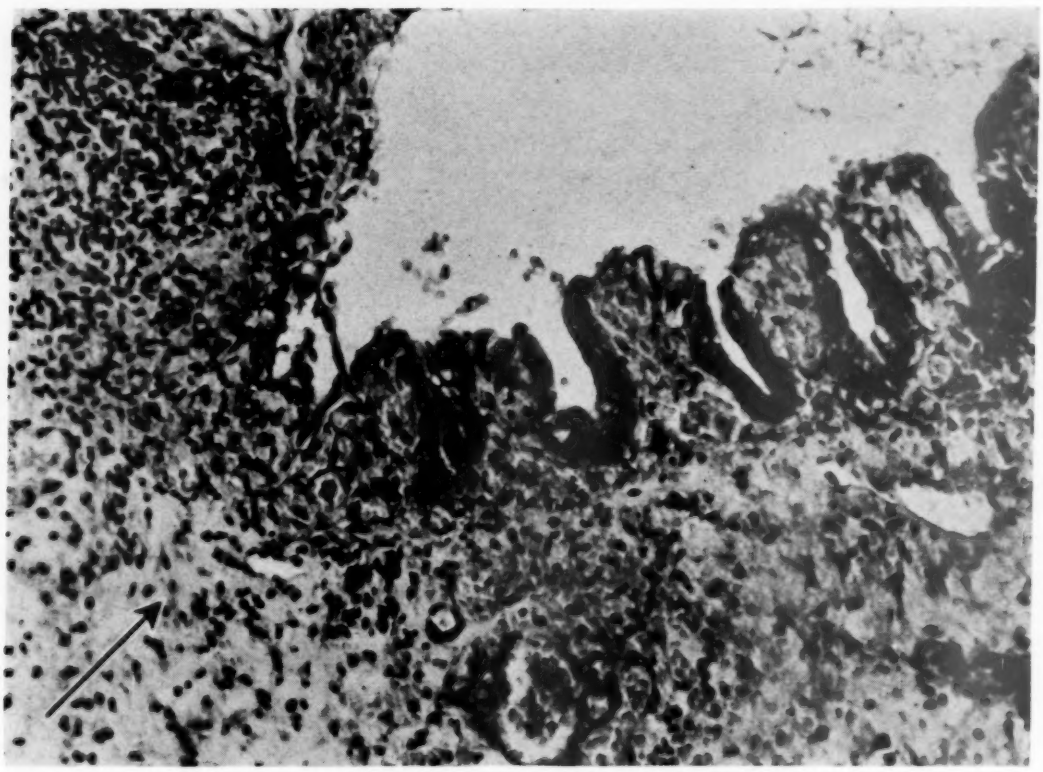

Fig. 3.—Photomicrograph of the biopsy taken from the margin of the perforation, showing the line of demarcation between the area of ischemic necrosis and normal mucosa. The entire width of the biopsy specimen was slightly less than 0.25 cm. Although the free margin of the perforation is not shown, the area of demonstrable necrosis is estimated to be not more than 0.015 cm. in width.

The meconium was drawn off with a suction tip as it escaped. The removal of the gas produced a pronounced deflation of the abdomen and there was comparatively little distention of either the large or small bowel as far as could be seen through the small incision. A cautious exploration promptly revealed a large perforation of the anterior wall of the cecum (Fig. 2). The margins were ragged and showed questionable necrosis in a few localized areas, but there was no frank gangrene and it was believed that this slight, patchy, marginal necrosis was consistent with spontaneous or traumatic rupture of eight to ten hour's duration. In retrospect, this was typical of ischemic rupture of the bowel, but not having previously encountered this condition, its importance was missed. A biopsy of this margin was taken and showed (Fig. 3) the extremely narrow area of the necrosis.

At this point it was believed that a diagnosis of traumatic rupture of the cecum was justified because:

1. The history of the trauma was definite, having been obtained from the obstetrician himself.

2. The appearance of the perforation seemed consistent with the diagnosis.

3. If obstruction due to congenital atresia were present it would have to be somewhere between the mid-ascending colon and the rectum, and atresia this low in the intestinal tract is extremely rare.

4. There was a clear history, taken from nursing notes, of five normal meconium stools, and though this did not exclude stenosis, rupture with stenosis is rare, if it occurs at all.

5. In the presence of widespread meconium peritonitis in an infant old enough to have bacteria in the meconium, general exploration of the abdomen was deemed unwise.

On the basis of this reasoning, the perforation of the cecum was closed transversely with Halsted and Lembert sutures of fine silk, and after removal of as much of the escaped meconium as possible, the abdomen was closed with through-and-through silver wires. No decompressive tube cecostomy was done.

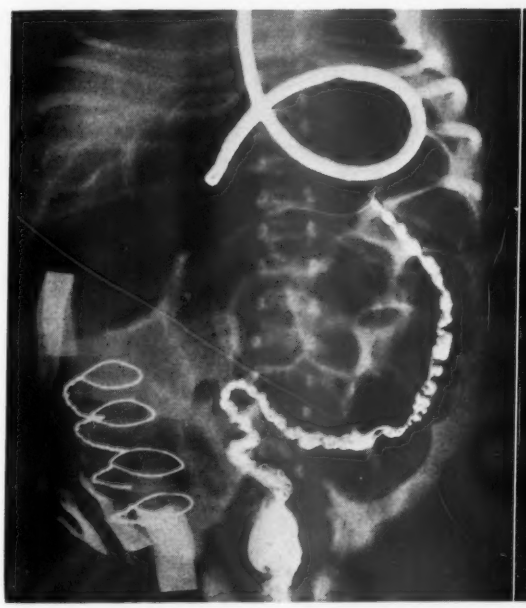

Fig. 4.

Fig. 5.

Fig. 4.—Barium enema after closure of the perforation. The silver wire closure of the first operation is seen in the right lower quadrant. The column of thin barium is seen filling the small, undistended bowel distal to the atresia and ending abruptly at the hugely distended transverse colon, just proximal to the splenic flexure.

Fig. 5.—Barium enema done two months after the first resection. The marked enlargement of the colon distal to the previous atresia is readily seen. However, a persistently narrowed segment, shown by the arrow, is producing partial obstruction. That this is more than a temporary peristaltic contraction is evidenced by the marked dilatation of the proximal colon and by the fact that the configuration was the same in two consecutive barium studies, both of which included direct barium contrast and postevacuation films.

The infant was continued on gastric suction and supportive parenteral fluids, but by the following morning distention was again quite pronounced and flat films showed multiple distended loops. Since the known perforation had been closed it was believed that a cautious barium enema should now be done (in spite of the risk to the suture line) to rule out possible atresia. The rapidly increasing distention seemed out of proportion to what might be expected from paralytic ileus associated with the meconium peritonitis and the trauma of the surgical procedure. The barium studies showed a striking narrowing of the entire descending colon (Fig. 4), and the column of barium was seen, under the fluoroscope, to stop abruptly at a point just proximal to the splenic flexure. It became apparent, therefore, that the history of normal meconium stools was entirely erroneous and that there was a congenital atresia at an unusually low level.

The patient was prepared for surgery at once and fourteen hours after the first operation, again under local anesthesia, the abdomen was opened through a transverse supraumbilical incision dividing the left rectus muscle. The small bowel was enormously distended and extruded through the wound. Decompression was effected through a needle attached to a rubber tube and brought out under water. The needle puncture was then buried under a purse-string suture. The point of atresia was easily identified just proximal to the splenic flexure. The transverse colon proximal to the atresia was enormously distended, and distal to this point the colon was about the size of an ordinary pencil. A short segment of bowel including the point of atresia was resected, taking a cuff of the dis-

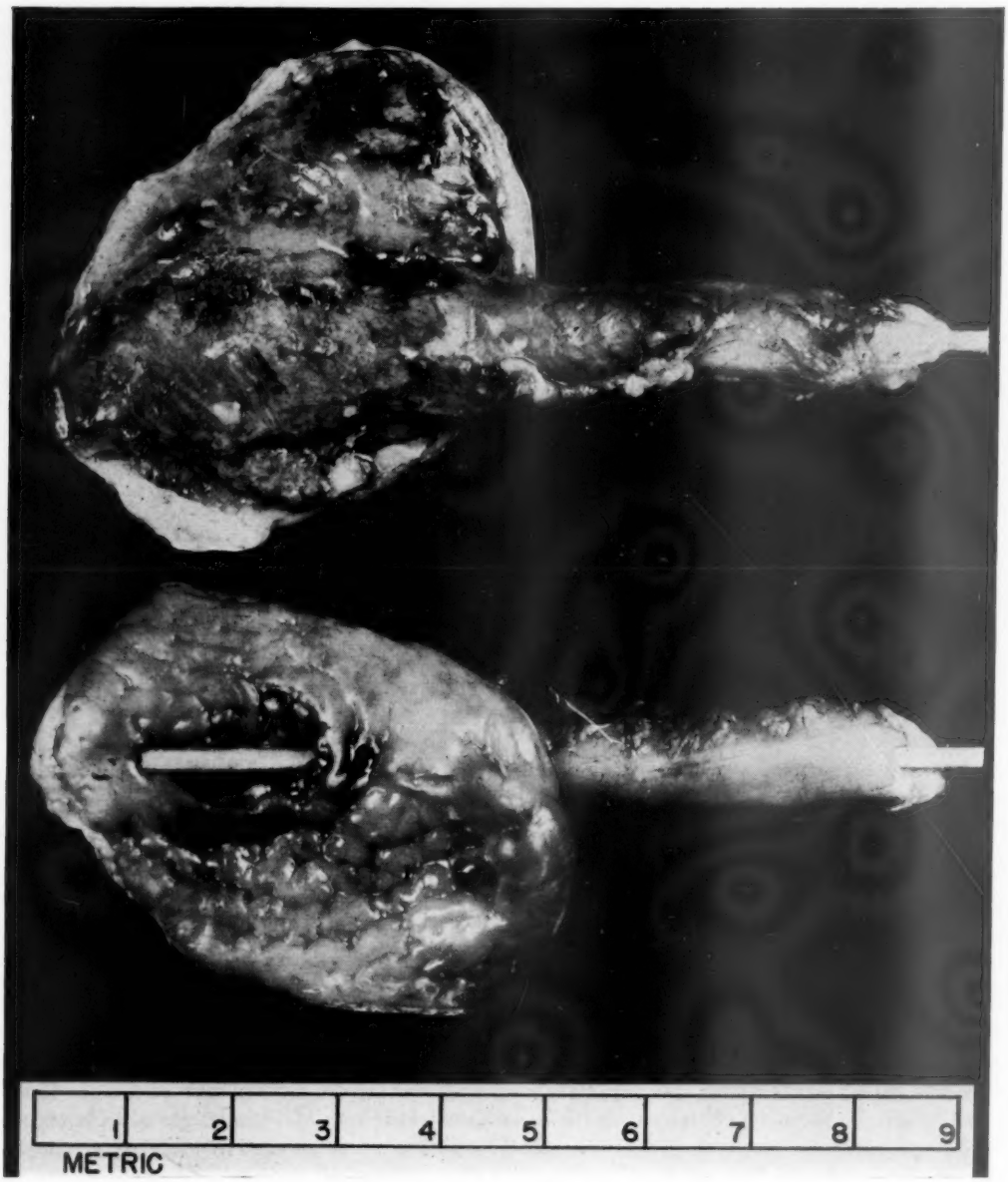

Fig. 6.—Specimen removed at the second resection and anastomosis. A wooden applicator stick has been passed through the specimen. In the lower photograph the exposed portion of the stick lies in the stoma of the first side-to-side anastomosis. This stoma was patent and adequate and much larger than the lumen of the narrowed distal segment.

tended bowel above and about 4 cm. of the collapsed bowel below (Fig. 2). A catheter was passed into the distal segment, which was irrigated with saline solution out through the anus to wash it free of barium. Both stumps were then closed and a side-to-side anastomosis was performed. The wound was closed with silver wire. The infant stood the procedure very well.

Gastric suction was continued and fluid, protein, and electrolyte balance were parenterally maintained with serum albumin, amino acids, whole blood, and saline solution, as indicated by continued laboratory studies. The expert attention of the pediatric staff was a decisive factor in bringing about a successful outcome. Penicillin and streptomycin were also administered.

Fig. 7.—Photograph of the patient at age of 4½ months. His nutritional state is good and he gives no evidence of abdominal discomfort, although the abdomen remains slightly protuberant.

On the fifth postoperative day the baby had the first small spontaneous bowel movements, though small returns had been obtained on the third and fourth day from mineral oil enemas. The gastric suction tube was permanently removed on the ninth postoperative day, though it had been removed for short periods beginning with the fourth postoperative day and replaced when there was evidence of distention. After the ninth day cautious oral feedings with glucose water, barley water, and finally formula were progressively offered and by the fourteenth day normal formula feedings were well tolerated. The wire sutures were removed on the sixteenth day and the infant was discharged home in good condition on the twenty-seventh postoperative day. During the last week the stools were essentially normal in all respects. The infant continued to do well at home. The appetite and gain of weight were satisfactory. Bowel movements remained normal.

Although the infant continued to thrive and gain weight, a barium enema done two months after operation revealed a disturbing situation (Fig. 5). The descending colon had increased appreciably in size, but the ascending and transverse colon remained grossly distended and a short segment about 4.5 cm. long, just distal to the anastamosis, remained markedly narrowed, producing a partial obstruction.

Fig. 8.—Barium contrast studies done one and two months after the second resection. The increase in size of the distal segment is apparent and approaches a normal configuration for a 4-month-old infant. The dilatation of the proximal segment is exaggerated by the fact that these films were made when the bowel was maximally distended with barium. The post-evacuation films, which are not shown, show a substantial decrease (about 40 to 50 per cent) in the diameter of the proximal segment as compared with films made prior to the second resection.

The infant was readmitted to the hospital on July 2, 1949, and on the day following a tube cecostomy was done under local anesthesia. Three days later, under general anesthesia, the previous transverse incision was reopened. Although there were numerous dense adhesions resulting from the previous operation and the peritonitis incident to the original perforation, these were carefully divided and the previous anastomosis was exposed. The narrowed segment and a cuff of dilated bowel proximal to it were resected (Fig. 6), and another side-to-side anastomosis was done. This was greatly facilitated by the fact that the distal bowel was now much larger than at the first resection and the proximal dilated bowel had been partially collapsed by preliminary cecostomy. The infant withstood both the third and fourth operations without difficulty and made an uneventful recovery. The cecostomy tube was removed on the seventh day after resection and the patient was discharged fourteen days after operation.

The patient was re-examined at intervals of one and two months after the last operation and continued to gain weight and do well clinically. At four months of age the weight had increased from 8 pounds 4 ounces at birth to 15 pounds. Frequency of formed stools had decreased from six to four a day. The abdomen was moderately protuberant, but the infant was reported by his mother to give no evidence by fretfulness and crying of any abdominal discomfort (Fig. 7).

However, contrast films taken at both follow-up visits showed that the large bowel, though improved, had not yet become entirely normal (Fig. 8). The proximal colon remained markedly dilated but was estimated to be 40 to 50 per cent smaller in diameter than in the film taken prior to the last resection. The distal colon had steadily increased in size and was approaching normal proportions. It is hoped that as the infant grows older the disproportion between the proximal and distal segments will be still further reduced.

Comment.—This case illustrates a number of important points. In the first place, it is unwise to assume, even in the presence of a distinct history of it, that trauma during delivery plays a significant part in rupture of the bowel in the newborn infant. The emphasis on the traumatic history, and the completely erroneous history that the infant had passed several normal meconium stools, as well as the appearance of the margins of the perforation at the first operation were misleading. A study of the literature indicates that trauma may be discounted as a significant factor. Although spontaneous perforation is known to occur, a safe rule is to assume, in the presence of perforation, that obstruction distal to it is present and must be treated. Further comment will be made on this point in connection with perforation in the presence of meconium ileus, but if the distal obstruction is found to be an atresia, resection and anastomosis is the procedure of choice. Without previous experience, the surgeon is tempted to perform an exteriorization procedure, since the appearance of the tiny bowel distal to the obstruction is such that one wonders how it can possibly dilate sufficiently to function as normal bowel. Ladd and Gross and others have warned against this temptation and have pointed out that the distal bowel is intrinsically normal and will function well if normal bowel contents can be made to reach it. This is an observation of the utmost importance, and failure to appreciate it has led to many needless failures in the surgery of this condition. However, all writers agree, and certainly it has been the experience in this clinic, that exteriorization procedures are poorly tolerated in early infancy and childhood. Naturally, as is true in adults, a small bowel enterostomy such as an ileostomy is more difficult to handle than a colostomy, and infants are especially vulnerable to the loss of fluid and electrolytes incident to this procedure unless it is followed as promptly as possible with a definitive procedure. The same is true of colostomy, though transverse and descending colostomies are naturally better tolerated. In another case similar to the one just described (if circumstances should prevent immediate resection and anastomosis), a decompressive tube cecostomy done at the first operation, followed by definitive resection and anastomosis as soon as the condition of the patient permits, would be much safer. This maneuver would certainly have been used in the case reported had we not been temporarily led into the mistaken belief that no distal obstruction existed. We regard it as a fortunate

accident that the suture line in the repaired cecum did not break down from distention between the first and second operations. A tube cecostomy was profitably used before the second resection and made that procedure considerably easier by reducing the disproportion between the two segments to be united.

A conclusive explanation for the persistence of the narrowed segment which necessitated the second resection is not available. Several possibilities might be suggested.

1. The persistent segmental narrowing might represent an achalasia due to congenital deficiency of the myenteric plexus. However, careful study of sections from the first and second specimens showed a normal myenteric plexus in both.

2. Although the lumen of the first anastomosis was patent and adequate, as seen in the resected specimen from the last operation, two or three silk sutures were found to have penetrated the mucosa and were in process of sloughing out into the bowel. Sections through these areas showed multiple foci of suppuration in the bowel wall, the sutures having acted as wicks to carry infection from the bowel into its wall. It has been suggested that such multiple small abscesses might induce an irritative spasm of the adjacent distal segment. This appears, at first, to offer a simple explanation of the phenomenon, but there are several reasonable objections to it. Penetration of the mucosa by silk sutures has frequently been observed in experimental anastomoses in dogs and probably occurs much oftener than is generally supposed in human intestinal anastomoses. Although the sutures always slough out, no spasm of the adjacent bowel segment has been observed. There was no evidence of spasm with the second anastomosis in the patient under consideration, though suture penetration could just as easily have occurred.

3. The most rational explanation appears to be one based on the accepted embryologic basis for atresia and stenosis. Both are supposedly derived from the same mechanism, namely failure of recanalization after the bowel goes through a solid phase during the fifth to tenth weeks of embryonic life. The difference is merely one of degree. There is no apparent reason why atresia and stenosis might not occur in the same bowel and even in the same segment. Clogg[11] implied that this does happen although a search of the literature has failed to disclose a specific instance of it. It is a common observation that stenosis may represent much more than a band-like constriction and may involve a considerable segment. In this connection Cole[13] said: "This type is frequently encountered, revealing a narrowing of the bowel over a variable distance. . . . Usually stenosis extends over a distance so great that an anastomosis is necessary to correct the defect."

The microscopic findings in a stenotic segment are not very characteristic unless the stenosis is so marked as to admit only a probe. Ladd and Gross stated that, "Microscopic examination of the narrowed zone shows heaped-up mucosa and submucosal folds which may be supported by accessory smooth muscles and irregularly distributed connective tissue. In those stenoses with only slight narrowing of the intestinal tube, microscopic examination of a longitudinal section may show little more than increased fibrous tissue in the submucosa or

muscularis.'' In the sections (both longitudinal and transverse) taken from the segment removed at the second resection in our patient, no abnormality of any kind, except the narrowed lumen, was demonstrated. This still does not exclude stenosis, because there are cases on record with definite stenosis of a considerable segment of bowel in which the microscopic sections are normal. For example, Boland[8] described a case of stenosis involving nearly one-half of the ileum in which ''microscopic section of this part of the intestine showed that its walls and glands were perfectly normal, like those of the rest of the ileum.'' This extensive stenosis, in which ''the lumen of the lower half of the ileum had a diameter of only 1.5 cm., about large enough to admit a lead pencil,'' was found at autopsy in a 44-year-old woman. She was the mother of two children and had enjoyed fair health most of her life except for occasional attacks of indigestion and vomiting. She died of peritonitis twelve days after a gastroenterostomy which was done under the impression that her symptoms were due to a duodenal ulcer. At autopsy the anastomosis was found to have leaked, but there was no prepyloric or duodenal lesion and the symptoms were apparently due to the long stenotic segment. It is of interest that the stenosis involved the middle half of the ileum and ''as the ileum approached the cecum it increased in size so that it was normal at the ileocecal valve.''

It seems reasonable to suppose, therefore, that a somewhat similar situation existed in our patient and that the segment which failed to dilate was stenotic. Webb and Wangensteen[38] recommended eighteen years ago that before the anastomosis is done after resection of an atresia, the distal segment should be dilated by isolating it between rubber-shod clamps and distending it with air injected through a hypodermic needle. This procedure should enable the operator to determine the distensibility of the distal segment since a stenosis would prevent successful dilatation. Employment of this maneuver in the first resection in our case might have prevented the need for the subsequent operation. The importance of Webb and Wangensteen's maneuver cannot be overemphasized in view of this experience.

To return to the cause and management of rupture of the bowel, mention should be made of those perforations in which the complete obstruction is due to meconium ileus. This condition is perhaps more common than is atresia, but associated perforation of the gut probably occurs in a smaller percentage of cases than it does when secondary to atresia. However, when perforation does occur, or when the condition is diagnosed before perforation, the management is quite different from that of atresia.

Meconium ileus was, until the recent report of Hiatt and Wilson,[20] regarded as uniformly fatal,[2, 9, 10, 16] and was so described by Hurwitt and Arnheim,[21] in 1942, and Swenson and Ladd,[35] in 1945. Hiatt and Wilson reported five recoveries (none of which was complicated by perforation) using a technique based on Farber's demonstration that the altered meconium in this condition can be quickly liquefied by contact with saline solutions of pancreatin.

Although we have not encountered such a case since Hiatt and Wilson's paper appeared, we believe that a discussion of rupture of the bowel would be incomplete without mention of their technique. These writers have shown that

the immediate surgical emergency is amenable to operation. Resection and side-tracking procedures have been repeatedly tried without success since the underlying pathology remains uncorrected. However, as Hiatt and Wilson emphasized, in those cases complicated by volvulus or otherwise devitalized bowel, resection must be done in addition to removal of the obstructing meconium. They have accomplished the latter procedure successfully by flushing the obstructed bowel free of inspissated meconium with saline solution through an enterotomy into which a catheter has been inserted and supported by a purse-string suture. When the bowel has been washed clean of all abnormal meconium, a solution of 5 per cent pancreatin is injected into it and the enterotomy is closed. The writers warn especially against the spilling of this powerful digestant outside of the bowel lumen. No transabdominal drainage or decompressive procedure is used. After operation pancreatin can be introduced by gastroduodenal intubation until bowel function is established, and thereafter medical treatment in the form of high protein, modified starch, low fat diet, along with various adjuncts to supplement the impaired tryptic activity of the pancreas and to prevent or control superimposed infections, must be continued. The ultimate outlook, even if surgical recovery is uncomplicated, is not as good in meconium ileus as it is after recovery from an atresia of the bowel. In the latter condition the patient may be restored to a normal state of health. In meconium ileus the child is still a victim of pancreatic insufficiency characterized by the so-called celiac syndrome, and in a high percentage of cases the associated pulmonary complications may prove fatal independently of the pancreatic disorder. As mentioned in the preliminary discussion, Farber believed that the disease is a systemic one not necessarily confined to the pancreas or lungs. The cause is unknown, though there is some evidence that Vitamin A deficiency or a functional impairment of utilization of this vitamin may play a part. At any rate, Farber believed that if the cause and specific therapy can be found, the pancreas is perfectly capable of regeneration and normal function, even if the pathologic changes are advanced and extensive. Moreover, with vigorous and meticulous medical care, some children with the celiac syndrome can be assisted to normal development and a reasonably normal life. Therefore, even though the ultimate outlook in cases of meconium ileus, with or without perforation, is not as good as in perforation or obstruction from other causes, this should not engender a defeatist attitude on the part of the surgeon, and every effort should be made to give these infants a chance to recover.

CONCLUSIONS

1. Perforation of the bowel in the newborn infant, though a rare condition, probably occurs more frequently than is generally supposed. It has carried an extremely high mortality, but it is believed that this rate can be reduced.

2. Obstetrical trauma is seldom a factor in rupture of the bowel in newborn infants.

3. Although "spontaneous" perforation in the absence of obstruction distal to the perforation does occasionally occur, it should be assumed in the presence

of perforation that obstruction is present until absolute proof to the contrary has been achieved.

4. The use of contrast media in the newborn infant for upper gastrointestinal films in the presence of obstruction, with or without perforation, is dangerous and should be avoided. Barium or Lipiodol enema may be helpful if used with caution and judgment and if all of the contrast media is removed after examination. The value of this roentgenologic procedure lies in the fact that the demonstration of a tiny, pencil-sized large bowel is virtually diagnostic of complete obstruction above, whether the actual location of the obstruction is demonstrated or not.

5. Where it can be proved that there is no obstruction in association with perforation, closure of the perforation is surgically adequate.

6. Where obstruction is due to atresia, resection and anastomosis should be done primarily if possible, or in the case of duodenal obstruction a sidetracking duodenojejunostomy should be done. If any case, continuity of the bowel should be established as soon as possible, and, where circumstances prevent definitive surgery at the first operation, a decompressive tube enterostomy may be used as a safety measure until bowel continuity can be restored. The prolonged use of enterostomies or exteriorization procedures is unwise and should be avoided if possible.

7. The use of the Webb-Wangensteen procedure to determine the distensibility of the collapsed bowel distal to an atresia is of fundamental importance in ruling out stenosis distal to the complete obstruction.

8. In perforation secondary to meconium ileus, resection of devitalized bowel should be done. If the bowel is viable, closure of the perforation is sufficient, provided that the bowel is first completely cleared of inspissated meconium and appropriate steps are taken to keep subsequent bowel contents in a normally fluid state. A tube enterotomy is necessary to clear the bowel, but enterostomy should be avoided.

9. Accurate diagnosis and appropriate surgery are essential, but supportive therapy both before and after operation is equally fundamental, and close cooperation between surgeon and pediatrician is prerequisite to a successful outcome.

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THE CURE OF HYPERTENSION BY NEPHRECTOMY

A Ten-Year Follow-up of a Case

Carl E. Burkland, M.D., Sacramento, Calif., Willard E. Goodwin, M.D., Baltimore, Md., and Wyland F. Leadbetter, M.D., Boston, Mass.

(From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital)

SINCE the work of Goldblatt[1] on producing experimental hypertension by interference with the renal circulation, there have been many clinical reports which record enthusiastic accounts of apparent cure or amelioration of hypertension by nephrectomy for unilateral renal disease. Few of these results have stood the test of time, as within a few months or a year after surgery the hypertension has returned.

For this reason it is important to present a ten-year follow-up of a patient who was treated by nephrectomy for hypertension in January of 1938 and who has maintained a normal blood pressure since. This case was first reported by Leadbetter and Burkland[2] in 1938, and later followed at three and one-half years after operation with a report by Burkland[3] in 1941. The case has frequently been listed as a "cure" in the literature on the subject since then.

The case (BUI 26839) was described in detail in the first report and will not be discussed completely here. Briefly, it is as follows.

CASE REPORT

The patient was a 6-year-old colored boy in whom hypertension had been present from the age of 6 months. Studies at the age of 3 years disclosed an ectopic pelvic kidney on the right side. There was no evidence of pyelonephritis or coarctation of the aorta. In December, 1937, urologic studies revealed very poor function in this right ectopic kidney. Because the experimental work of Goldblatt suggested a relationship between the abnormally situated, poorly functioning kidney and the hypertension, and since the blood pressure had been persistently elevated, when the patient was 5½ years old, a right nephrectomy was carried out by one of us (W. F. L.). On Jan. 26, 1938, a hypoplastic, ectopic pelvic kidney, in which the main artery was partially occluded by a mass of smooth muscle, was removed. This intra-arterial mass of smooth muscle, thought to be congenital, presented on microscopic section a picture similar to that seen in some of Goldblatt's cases in experimental animals where the main artery was partially constricted by a specially devised clamp (see Fig. 1). Following nephrectomy the blood pressure fell promptly to normal and has remained so ever since.

Before operation the blood pressure averaged 155/105; one year after operation it was 120/75, two years after operation 110/70, three and one-half years after operation 105/64, seven years and three months after operation 104/74 in the left arm and 104/78 in the right arm, and ten and one-half years after operation 136/80 in the right arm and 130/76 in the left arm (see chart, Fig. 2). He was very carefully observed in 1945 and again recently, and the results show that he has grown normally with no symptoms or signs of cardiac or renal disease.

Our observations on Sept. 11, 1948, were as follows. Physical examination revealed a well-developed, well-nourished, 16-year-old colored boy, weight 126 pounds, height 5 feet 4 inches, blood pressure 136/80 (right arm) and 130/76 (left arm), and pulse 56. Laboratory findings were: hemoglobin 13.6 Gm. per cent; hematocrit 41.4 mm.; white blood count 6,800 per cu. mm.; sedimentation rate 3.0 cm. per hour; icteric index 9.0; and

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differential, smear, and platelets normal, with no evidence of sickling. Urinalysis showed specific gravity 1.030, albumin –0, sugar –0, and microscopic examination negative, except for crystals. Urine culture was sterile. Blood nonprotein-nitrogen was 25 mg. per cent.

Intravenous urograms showed a "normal," somewhat hypertrophied left kidney, a normal bladder outline, and no evidence of a right upper urinary tract.

Chest studies, fluoroscopy and teleoroentgenogram, carried out by the x-ray department* were reported as follows: There was a calcified node in the right hilum. The long diameter of the heart was 13.5 cm. The short diameter of the heart was 10.6 cm., giving a frontal plane measurement of 92 cm. The predicted frontal plane area was 95 cm., giving a variation from the normal of 3 per cent. On fluoroscopic examination, the heart pulsated slowly and regularly. There was no definite evidence of chamber enlargement. The lung parenchyma showed no evidence of active tuberculous infiltration. The bony thorax was within the limits of normal. The impression was calcific focus, right hilum. No evidence of hypertensive heart disease or of lung pathology was found.

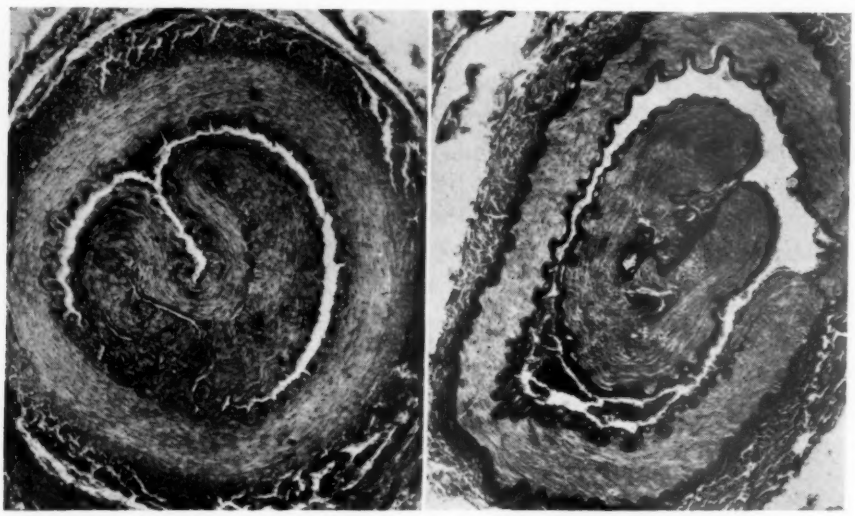

Fig. 1.—*A*, Cross-section view of main renal artery, showing its partial occlusion by a smooth muscle plug; *B*, cross section of renal artery close to kidney, showing particularly internal and external elastic lamellae of vessel which are lost at the point where vessel wall is thinned out (stained with van Gieson's tissue stain).

Comment.—We believe that this case represents a definite cure by nephrectomy of hypertension caused by unilateral renal disease. It is the only case in the literature followed ten years after operation. Sabin[4] published a complete review of the literature up to 1948 in regard to the results of nephrectomy for hypertension. In an analysis of 101 cases he found that in fifty-one the blood pressure returned to normal, although twenty-one had been followed less than a year since the time of operation; in twenty-three there was a reduction in blood pressure, but not to normal levels, and in twenty-six no improvement was obtained. He found that the commonest pathologic condition in these cases was chronic pyelonephritis, in which the kidneys frequently showed marked atrophy. In only sixteen of these cases had the blood pressure following surgery been observed for two years or more. Braasch[5] found that, at the Mayo Clinic, the incidence of unilateral renal disease in patients with hypertension who were amenable to treatment was only 0.5 per cent, and that the hypertension in

*By Dr. D. M. Gould.

such patients had frequently been relieved by operation. He found the most amenable lesion to be atrophic pyelonephritis. In January, 1949, Gasue, Glasser, and Grossman[6] reported a case of extreme hypertension in a 1-year-old girl cured by nephrectomy. Their patient, who had a unilateral atrophic pyelonephritis, was followed for two years. They could find in the literature only nine cases in children in which the blood pressure had remained at normal level for at least one year following the operation.

We can conclude that the actual number of reported cases in which hypertension is associated with unilateral renal disease is not large, and that in only a small percentage of these can a definite etiological relationship be established between the vascular lesion and the elevation of the blood pressure. In our personal clinical experience we have not found another case similar to the present one.

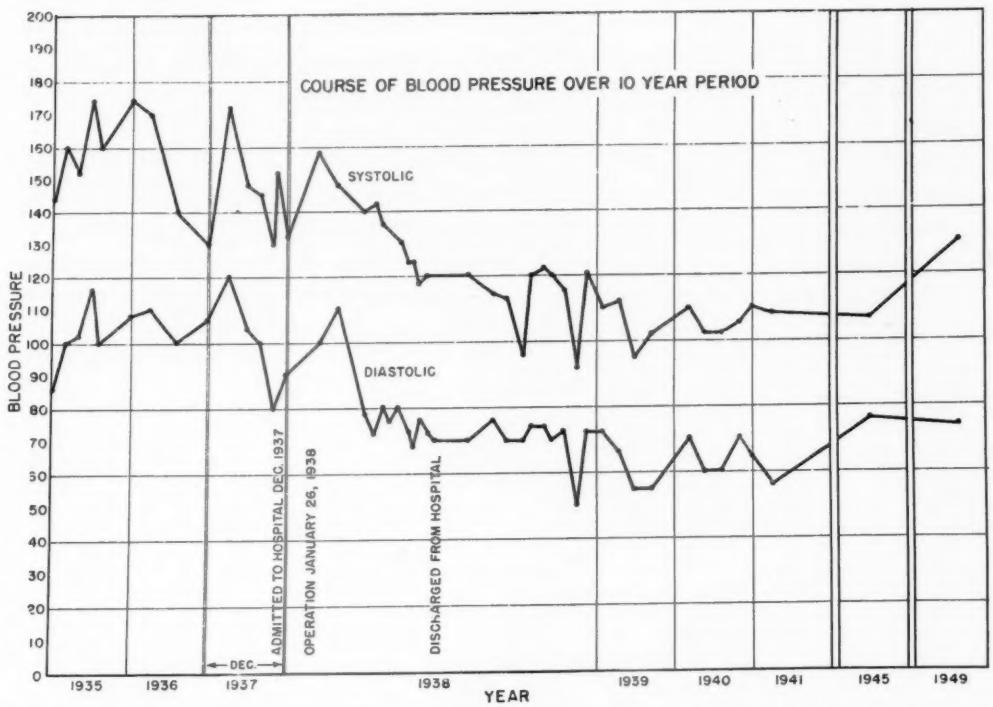

Fig. 2.—Chart showing course of patient's blood pressure before and for ten and one-half years after surgery.

The rather low percentage of cure reported in the literature in our opinion has been due to the poor selection of cases for operation. We believe that, using the premise of Goldblatt's work, the emphasis should be placed on locating a lesion of the main renal artery, either intrinsic or extrinsic, which might produce interference with the renal circulation and cause an elevation of blood pressure.

In the majority of cases reported in the literature in which relief of hypertension by nephrectomy has been obtained, the lesion has been one of chronic pyelonephritis. This condition, like hydronephrosis, is often bilateral. Even with our present methods of examination it may be difficult to determine that

the opposite kidney is absolutely normal in function and free of any infection. We feel that a search for more strictly vascular lesions, particularly of the renal artery or its main branches, should be made. It may be that aortography[7] would give this information. The current theories of the humoral mechanism of hypertension are expressed by Corcoran[8] and by Goldblatt.[9]

In consideration of the work of Goldblatt and others and the rather poor results of nephrectomy for hypertension which have been reported, the criteria laid down by Sensenbach[10] for the selection of patients with hypertension for whom nephrectomy is indicated seem very valuable to us. They are: (1) The diseased kidney should be functionless or its function greatly diminished; (2) the opposite kidney should function normally; (3) the hypertension should be of short duration; and (4) other factors being equal, the younger the patient, the greater the chance of favorable results following nephrectomy.

SUMMARY

A ten and one-half year follow-up of a colored boy treated by nephrectomy at the age of 5½ years for severe persistent hypertension is presented. He is an apparent "cure."

Scrutiny of the literature reveals only a few cases cured or benefited by nephrectomy for unilateral renal disease. This is probably due to the fact that not many cases with unilateral interference of the renal circulation exist, or that they are not discovered sufficiently early for a good result from surgery. Particular attention to the criteria laid down by Sensenbach for selection of cases will probably lead to better results in the future.

ADDENDUM

Since this paper was accepted for publication we have new observations, which were made on May 19, 1950, twelve years and five months after operation. They revealed a normal-appearing, 18-year-old colored boy weighing 140 pounds, with a blood pressure of 132/80 in the right arm while lying down, normal pulse rate, and normal urinalysis.

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WRINGER INJURY

PAUL F. HAUSMANN, M.D., AND HARRY H. EVERETT, M.D., MILWAUKEE, WIS.

(From the Surgical Service of The Milwaukee Children's Hospital)

THE subject of wringer injury, or wringer arm, has been neglected both in the literature and in the standard texts of surgery. As a result, the average physician and general surgeon seeing this type of injury for the first time is unaware of its serious nature. Only too often the treatment used is inadequate or even damaging. The number of neglected and mishandled cases which have come to our attention focus the need for a paper covering the proper treatment of this form of injury.

The modern semiautomatic washing machine is equipped with an electrically operated wringer. The majority of these wringers have safety devices which, if tripped, release the roller pressure. Children, especially the very young, are fascinated by moving machinery. Sooner or later, if not watched, probing fingers are caught in the turning rollers. The wringer overpowers the screaming child and draws a portion or all of the arm into the machine. If the child is fortunate, the rescuer stops the motor and sets off the safety release. Unfortunately, however, the wringer is usually reversed and the arm is rolled out, resulting in additional injuries. Should rescue be delayed, the wringer mechanism will churn at either the elbow or axilla, causing severe injuries to the underlying vessels and nerves. Upon release, the child is immediately rushed to the nearest physician or hospital. It is at this stage that the treatment is often mismanaged.

TRUE SURGICAL EMERGENCIES

Wringer injury is considered and treated as a true surgical emergency at Milwaukee Children's Hospital. A careful history as to the method of production, extent, and length of time since the onset of the insult is recorded. On first examination, the arm appears only slightly damaged. A few superficial abrasions, lacerations, ecchymoses, and a moderate amount of edema may be all that is noted by the examiner. When "churning" has occurred, there is usually a "brush burn" type of injury in the antecubital fossa or axilla, and varying amounts of skin may be destroyed or avulsed. The exact degree of superficial and deep tissue destruction, however, is difficult or impossible to estimate at the first examination, since the most serious element of the injury is hidden beneath the skin surface. This consists of a crushing type of injury to the underlying soft tissues—the muscles, tendons, nerves, and the blood vessels. The amount of ecchymosis and edema is trifling at first and may lead the examiner to the conclusion that the damage is confined to the superficial lesions. Within a few hours, however, the underlying soft tissues undergo a process of ischemic necrosis by reason of hemorrhage into the fascial planes, extravasation of blood and tissue fluid, and vascular spasm. These serious changes in tissue viability begin immediately and progress to an alarming degree within the first

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twenty-four hours. If progressive soft tissue damage is to be avoided, treatment must be instituted at the earliest possible moment. Progressive damage, however, can be prevented or lessened even after thirty-six hours. The end result of a mishandled case presents an extensive loss of muscle, tendon, nerve, and even bone. In addition, infection may supervene at any time in the devitalized tissues, thereby increasing tissue loss. Ischemic necrosis is the most damaging yet preventable component of wringer injury. Early and proper therapy must be used in order to avoid the serious consequence of deep tissue destruction. As a matter of fact, the entire purpose of our form of therapy is to prevent this process.

CLINICAL MATERIAL

The material for this study was taken from the files of the Milwaukee Children's Hospital, covering the period from January, 1935, until June, 1949. It includes a total of ninety-seven patients who were under the care and direction of eight surgeons. Forty-five of the patients (1935 to 1941) were treated by methods which were current during that period. They consisted of many of the following practices: hot compresses, multiple incisions, aspirations, cold packs, Dakin's solution irrigations, and Neoprontosile. These methods are now outmoded and many of them are considered bad surgical technique in the light of present knowledge. Especially bad is the application of hot compresses, since it hastens the destruction of tissue already partially devitalized. In 1942, the treatment of wringer injury at this hospital was standardized.[6] Since that date, the remaining fifty-two patients have been treated with the new method by the surgeons in charge and by the resident staff.

TREATMENT

After comparing the results of the periods just mentioned, we have found that the immediate application of pressure dressings is the treatment of choice. On admission to the hospital roentgenographic examination of the injured extremity is done in order to rule out possible fractures. If they are present, reduction is accomplished at the same time that the pressure dressing is applied. The injured extremity is cleansed thoroughly (ten minutes) with soap and water under aseptic precautions, preferably in the operating room with the operator wearing cap, mask, gown, and sterile gloves. Anesthesia is employed if necessary, but has been required in only a few instances. Superficial and deep lacerations are repaired in the usual manner. Any large hematomas are evacuated by aseptic aspiration. Sterile Furacin or petrolatum strips are applied lengthwise (not circularly) on the abrasions and repaired lacerations. A pressure dressing of Kerlix roll bandage is wound about the extremity so as to extend from the fingertips to well above the site of injury. We have discarded the use of mechanics waste as it is difficult to apply evenly. The outer layer of the dressing consists of rolled cotton elastic (not rubberized) bandage. The fingertips are left exposed to enable the physician to observe, at all times, the circulatory status of the extremity. Several layers of gauze are interposed between the fingers to avoid skin-to-skin contact. This type of dressing, since it is elastic,

TABLE I. POINT OF MAXIMUM INJURY (PERIOD FROM 1935 TO 1941)

REGION	NUMBER OF CASES	SLOUGH	SKIN GRAFT	FRACTURES
Hand	10	6	3	6
Forearm	13	4	5	3
Antecubital fossa and above	11	13	7	2
Axilla	12	7	5	0
Axilla and chest	2	4	2	1
Totals		34	24	12

Deaths	2
Amputations	0
Number of cases	45
Sex	
Male	28
Female	17
Side involved	
Right	31
Left	11
Both	3

gives support to the damaged vessels and prevents further edema and extravasation. Should a fracture be present, a light plaster cast may be applied in order to maintain reduction.

The forearm and arm, following the application of the pressure dressing, are elevated and surrounded with ice packs. Procaine-penicillin (400,000 units) is given daily. Additional supportive therapy may be employed as indicated. This includes whole blood transfusions in amounts appropriate for age and weight. At times tetanus antitoxin may be indicated.

RESULTS

The use of pressure dressings and antibiotics has consistently given superior results since 1942. It has not been necessary to apply skin grafts in as many cases during this latter period due to a marked reduction in the amount and extent of tissue slough. The number of days of hospitalization has also been reduced.

TABLE II. POINT OF MAXIMUM INJURY (PERIOD FROM 1942 TO 1949)

REGION	NUMBER OF CASES	SLOUGH	SKIN GRAFT	FRACTURES
Hand	12	7	3	4
Forearm	20	2	2	2
Antecubital fossa and above	11	7	4	1
Axilla	8	2	2	1
Axilla and chest	1	0	0	0
Totals		18	11	8

Deaths	0
Amputations	1
Number of cases	52
Sex	
Male	36
Female	16
Side involved	
Right	31
Left	21
Both	0

The extent and severity of the injury were found to be similar for the two periods. It was also noted that wringer injury was twice as prevalent in males. During the period 1935 to 1941 there were two deaths. One death was due to hemolytic streptococcus septicemia and the other to a purulent tracheobronchitis. There were no deaths in the 1942 to 1949 period; however, one case required amputation of the arm immediately above the elbow. The latter case had been mishandled before reaching us, having received hot compresses as treatment for a period of thirty-six hours. On admission, a "brush-burn" in the antecubital fossa had already become markedly edematous and indurated, shutting off arterial pulsations at the wrist. The extremity was cyanotic and lifeless.

The data in Tables I and II summarize the findings for the two periods.

In comparing the average length of hospitalization for the two periods, it is obvious that a marked improvement has occurred following the adoption of the pressure dressing technique. The patients were grouped into those receiving immediate treatment (within twenty-four hours), and those in whom more than twenty-four hours elapsed before adequate medical care was instituted. Hospital days were reduced fifty per cent in the delayed cases; while those receiving immediate treatment had their hospitalization cut one-quarter. In a few cases the use of the antibiotics during the past seven years has helped reduce hospitalization where infection was a factor; however, in the majority, the wounds during both periods remained clean.

TABLE III. AVERAGE NUMBER OF DAYS OF HOSPITALIZATION

1935 to 1941	
Immediate treatment	16 days
Delayed treatment	65 days
1942 to 1949	
Immediate treatment	13 days
Delayed treatment	31 days

SUMMARY

1. At Milwaukee Children's Hospital the pressure dressing technique has been adopted as routine therapy for those cases sustaining wringer injuries.

2. Skin grafts are applied at the earliest moment in order to avoid the heavy indurated scars which follow long granulating wounds.

3. There has been a decided improvement in the functional and cosmetic results following the use of this technique.

4. The average length of hospitalization has been reduced in those cases receiving immediate treatment and also those whose treatment was delayed.

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THE EOSINOPHIL RESPONSE TO SURGICAL TRAUMA

WILLIAM R. COPPINGER, M.D., AND MARTIN G. GOLDNER, M.D., FORT LOGAN, COLO.

(From the Medical Research Laboratory of the Veterans Administration Hospital, Fort Logan, Colo., and the University of Colorado Medical Center, Denver, Colo.)

IT IS well recognized that surgical trauma, like any situation which induces the "alarm reaction," puts stress upon the adrenal cortex. The functional state and the responsiveness of this endocrine organ determine to a large extent the ability of the organism to sustain traumatization and the readiness of adaptation.

The eosinophil response is a simple test to measure the adrenal cortical reserve. This test was first described by Forsham, Thorn, Prunty, and Hills.[1] Working with the adrenocorticotrophic hormone of the pituitary (ACTH), these authors discovered that in the presence of a normal adrenal cortex a marked fall of the circulating eosinophil cells will occur after the administration of an adequate dose of ACTH. This eosinopenia develops within 2 to 4 hours and amounts to 50 per cent or less of the original level. In adrenocortical insufficiency, the eosinophil response is less marked or totally absent. Other stimuli of the adrenal cortex, as epinephrine,[2, 3, 4] insulin,[3, 4] and stress,[4] have also been shown to be attended by a decrease in the circulating eosinophils. These stimuli are transmitted to the adrenal cortex through ACTH. The eosinophil response to stress, therefore, indicates the functional state of the adrenal cortex only if the pituitary is normal.

We have followed the eosinophil response in patients who underwent various types of surgery. This study was done in an attempt to evaluate both the degree of stress exerted by various operations and the readiness with which adaptation occurs in various types of patients. While this work was in progress, Laragh and Almy[4] reported their observations in 15 surgical patients, all of whom showed marked eosinopenia 3 to 8 hours after the beginning of surgery. Our own results are in general agreement with these findings and add some data about the relationship of the eosinophil response to the severity of the surgical procedure and to the age of the patient.

METHOD OF STUDY

A consecutive series of 50 male surgical patients was studied. The surgical procedures were either elective or emergency operations and ranged from minor biopsies of skin or lymph nodes to major surgery such as pneumonectomy or portal-caval shunt. None of the patients were known to have adrenal cortical or pituitary insufficiency or showed signs or symptoms of Addison's disease. The age of the patients ranged from 20 to 68 years.

The method of counting the eosinophil cells was that described by Thorn and his associates,[1, 2] a modification of the Dunger method. Counts were taken preceding the operation, immediately following the operation, and thereafter at 24 hour intervals until the preoperative level was regained. The eosinophil

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response was calculated and expressed as the percentage of decrease or increase from the preoperative level of the circulating eosinophils, this being set as 0. In a first group of patients, the preoperative level was determined on several successive days. When it had become apparent that no appreciable changes occurred preoperatively, only one preoperative count was taken in the rest of the patients.

All patients were checked carefully with regard to blood pressure, general blood count, blood loss, and so forth, during and after surgery. No attention was paid in this study to the type of anesthesia employed.

RESULTS

The Preoperative Eosinophil Level.—Our values of the preoperative eosinophil count ranged from 11 to 718 per cu. mm., but only 5 values were below 100 and only 4 above 300. Forty-one out of our 50 patients showed preoperative levels between 100 and 300, with an average of 230. This is in agreement with the observation of others[1, 2, 4] who have reported the normal circulating eosinophil level as ranging between 100 and 300 per cu. mm.

The 5 patients with preoperative levels lower than 100 showed values of 11, 28, 43, 78, and 89, respectively. All of them had been admitted in acute emergency conditions, 2 with perforated abdominal viscus, 1 with acute exacerbation of ulcerative colitis, and 2 with frozen extremities and in starvation after 8 to 10 days exposure to a winter blizzard. It is reasonable to assume that these low counts already represented an eosinophil response to the trauma of the disease and cannot be considered as normal levels. Indeed, this is borne out also, as will be shown, by the fact that values far higher than preoperatively were obtained in these patients in the recovery period.

Extremely high preoperative levels of 352, 407, 518, and 718 per cu. mm., respectively, were found in 4 patients who had been under treatment with antibiotics, streptomycin (in 3 instances), and penicillin (in 1 instance). Here, the normal eosinophil count had probably been elevated by this therapy.

The Eosinophil Response.—In reporting in general the eosinophil response to surgical trauma, it seems advisable to differentiate between those patients whose preoperative eosinophil count had been well within the physiologic range and the aforementioned group of 9 patients, in whom either abnormally low or abnormally high preoperative levels had been found.

Out of the series of 41 patients with normal preoperative eosinophil levels, 35 showed a characteristic decrease of their circulating eosinophils during the postoperative phase. This decrease was already significant in most instances immediately after surgery, but became even more marked during the first postoperative day, when in most patients the lowest level was reached. Very few patients continued to show extremely low counts at the second postoperative day. In the majority of patients, however, the count 48 hours after operation indicated a gradual increase of the circulating eosinophils and a return to normal or slightly higher than normal levels which were reached at the third or fourth postoperative day. The 2 instances in which this return was markedly delayed or interrupted by a secondary decrease will be discussed later.

Five of these 41 patients, however, did not follow this pattern; 2 did not show any change at all, while 3 responded to surgery with a moderate increase of their circulating eosinophils.

Table I demonstrates the percentage change of the eosinophil count in this group of 41 patients. The immediate postoperative decrease averaged 33 per cent, the greatest decrease at 24 hours after surgery amounted to an average of 72 per cent, and two days after operation 22 patients showed still a decrease of more than 20 per cent with an average of 30 per cent for the whole group. On the third postoperative day a decrease of more than 20 per cent was found in only 11 patients, with an average of –18 per cent for the whole group. On the fourth day most patients had returned to their preoperative levels, and counts were taken in only 30 patients. Of these only 4 were significantly decreased.

The patients with abnormally high preoperative counts showed a less marked but otherwise identical curve of their eosinophil response. The lowest levels were reached 24 hours after operation, but did not exceed –30 per cent. The high preoperative levels were established during the second or third postoperative day.

TABLE I. THE EOSINOPHIL RESPONSE TO VARIOUS TYPES OF SURGICAL TRAUMA OF 41 PATIENTS WHOSE PREOPERATIVE LEVEL OF CIRCULATING EOSINOPHILS HAD BEEN WITHIN THE PHYSIOLOGIC RANGE

PERCENTAGE OF CHANGE IN EOSINOPHIL COUNT	NUMBER OF PATIENTS WITH GIVEN PERCENTAGE OF CHANGE IN TIME PERIODS AFTER SURGERY				
	IMMEDIATELY	24 HOURS	48 HOURS	72 HOURS	96 HOURS
+21 to + 40	0	0	0	2	3
+ 1 to + 20	3	4	3	6	4
0	2	1	3	6	12
– 1 to – 20	8	0	13	16	7
–21 to – 40	17	7	5	3	1
–41 to – 60	5	6	8	2	1
–61 to – 80	4	10	6	5	2
–81 to –100	2	13	3	0	0
Total number of patients	41	41	41	41	30*
Average per cent fall	33	72	30	18	–

*At 96 hours after operation counts were taken in only 30 patients, mostly those whose values had not returned to normal previously.

In contradistinction, the 5 patients with extremely low preoperative eosinophil counts, although showing a further decrease immediately and 24 hours after surgery, developed during the recovery phase eosinophil levels which were 5 to 10 times higher than prior to the operation. This seems to be further evidence for the assumption that their original low count reflected the acuteness and seriousness of their clinical condition. The final postoperative levels in these patients were well within the physiologic range.

Relationship of Eosinophil Response to Duration and Severity of Surgical Procedure.—Long-lasting or severe operations were attended by a more marked and prolonged eosinopenia than minor and short-lasting procedures. The 2 cases in which no eosinophil response at all was noted belonged to this latter group; both patients underwent lymph node biopsies. Fig. 1 demonstrates the eosinophil

responses as related to the operative time. The whole series was subdivided into 4 groups with operative times of less than 1 hour, 1 to 2 hours, 2 to 3 hours and more than 3 hours. Thirteen patients belonged in the first group, 18 patients in the second group, 9 in the third group, and 10 in the fourth group. It can be noted that the curves of the average eosinophil response become progressively deeper and prolonged from group 1 to group 4.

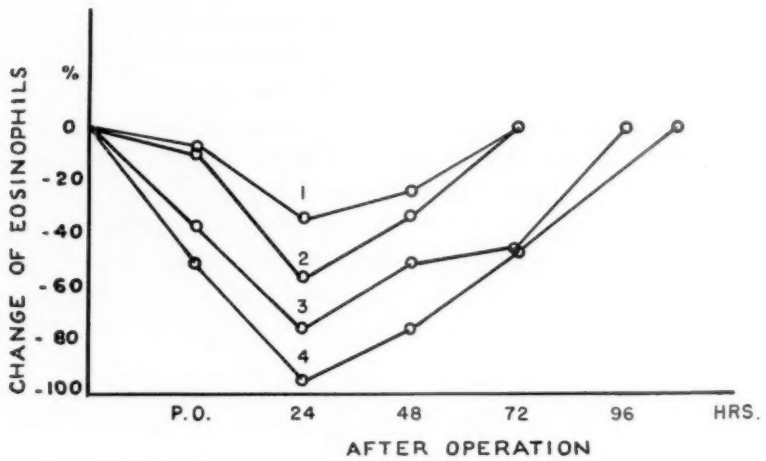

Fig. 1.—The eosinophil response in relation to the duration of the surgical procedure. Group 1 operative time less than 1 hour, Group 2 operative time 1 to 2 hours, Group 3 operative time 2 to 3 hours, Group 4 operative time more than 4 hours.

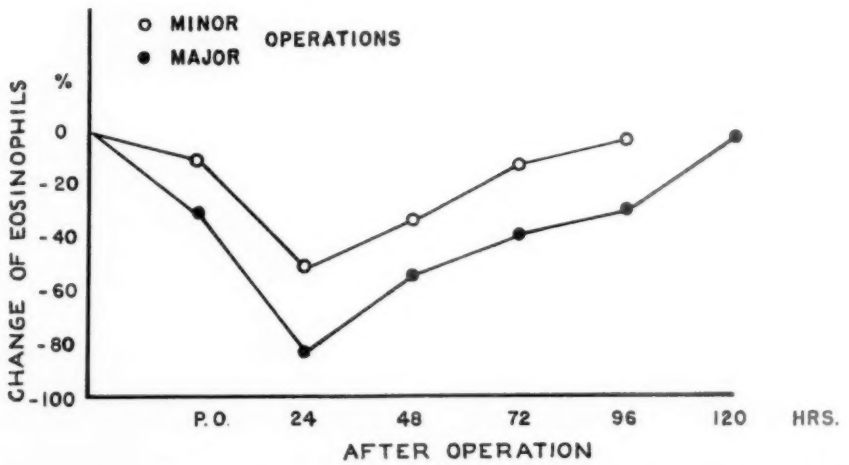

Fig. 2.—The eosinophil response in relation to the severity of the surgical procedure.

The operative time is only a crude index of severity of the surgical procedure. Therefore a grouping according to major or minor surgery was done. This is shown in Fig. 2, which demonstrates that the minor procedures were followed by a reaction which was shorter lasting and less marked than that after major surgery. Among the various major surgical procedures, the operations involving the liver and bile system seemed to have caused the most severe re-

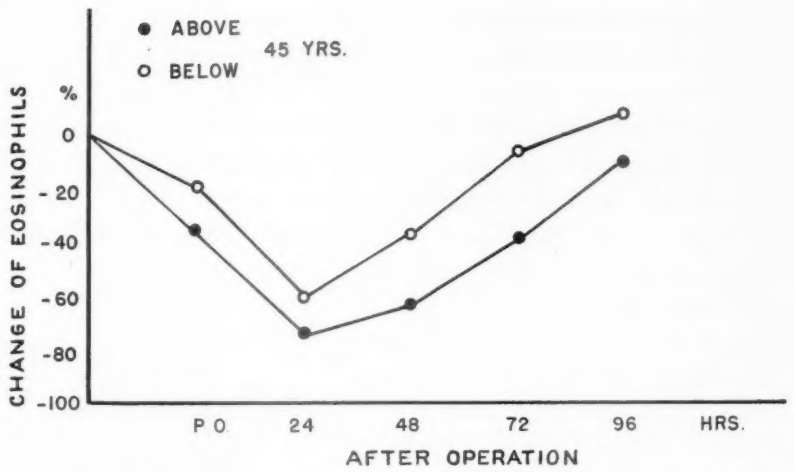

Fig. 3.—The eosinophil response to surgical trauma in relation to the age of the patient.

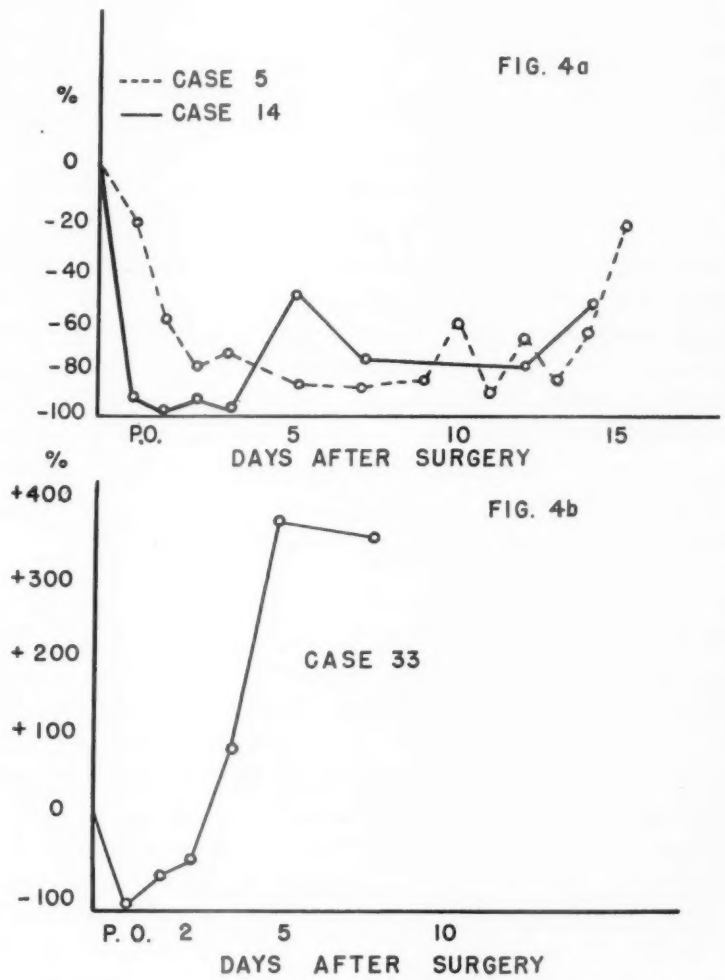

Fig. 4, *a* and *b*.—The eosinophil response to surgery in patients with *a*, postoperative, and *b*, preoperative complications.

sponses, with total disappearance of circulating eosinophils immediately postoperative, while the chest and brain operations were followed by a marked but less severe eosinopenia.

Age and Postoperative Eosinophil Response.—Our series of patients can be divided into 2 almost equal groups, those below 45 years of age and those above; 27 patients belong in the former, 23 patients in the latter. Since the surgical procedures performed on each group were rather similar, the eosinophil response in the 2 age groups should be comparable. This is demonstrated in Fig. 3. It appears that the older age group responded with greater readiness than the younger group, but the younger group returned to preoperative levels sooner than the older group.

The Eosinophil Response in Surgical Complications.—Two patients developed postoperative complications. These were the only 2 instances in which the eosinophil response was prolonged over the fifth day. One patient (Case 14) underwent a retropubic prostatectomy for benign prostatic hypertrophy. The operation was uneventful, but a severe septicemia developed on the second postoperative day. The septicemia was controlled and there was a beginning rise in the eosinophil count. However, a supervening epididymitis induced a second depression of the count in this patient. Another patient (Case 5) showed a similar reaction when, following a lobectomy performed for pulmonary tuberculosis, he developed atelectasis and pneumonia. The course in these 2 patients is demonstrated in Fig. 4 *a*. Undoubtedly the delayed return in these 2 patients indicated continuous strain on the adrenal cortex by the complicating conditions.

In comparison, Fig. 4 *b* shows the changes in the circulating eosinophils in a patient who was admitted as an emergency with a preoperative complication. This patient belonged to the aforementioned group with extremely low preoperative level. He suffered from a perforated appendix with localized peritonitis. His abnormally low admission count of 27 eosinophils per cu. mm. was interpreted as response to the acute onset of the illness. Immediately after operation the count fell to 0, but in the recovery phase he returned to a level of 125 per cu. mm., or about 400 per cent of the original level.

DISCUSSION

It is likely that the eosinophil response to surgical trauma depends on numerous factors of those which are involved in the complex mechanism of the surgical situation. No doubt the defense mechanism of the adrenal cortex as indicated by the eosinophil response may be influenced directly or indirectly by emotional and physical stress and strain, the underlying disease, the preoperative condition of the patient, age and perhaps sex, the preoperative treatment, the anesthesia, the type of surgery, the blood loss and blood substitution, to name some of them. Only a very few of these factors have been considered in this study. It has been found that the degree of the eosinophil response is related directly to the severity and duration of the operation, and to a certain extent to the age of the patient. Furthermore, it was seen that complications prior to or after surgery are reflected in the level of the circulating eosinophils.

Since the eosinophil response is related to the severity of the operation, it is evident that a negative response, as was found after minor operations, may indicate that the trauma was of insufficient magnitude to stimulate the adrenal cortex rather than that the adrenal cortex was deficient in its response. On the other hand, a failure of the circulating eosinophils to decrease in numbers in the course of a severe operation might foretell imminent adrenal cortical failure which would call for substitution therapy. Similarly, a slow and delayed postoperative return of the eosinophil count to normal levels may indicate prolonged adrenal cortical strain and danger of exhaustion. Here, too, substitution therapy should be considered.

It may be argued that during surgery the determination of the eosinophil response may have little diagnostic value because the symptoms of acute adrenal failure are easily recognized and require immediate treatment. However, prognostically, valuable information can be gained from the preoperative use of the eosinophil response if use is made of a test dose of epinephrine. It has been shown that the response to surgical trauma is the same as that to ACTH or epinephrine. Thus a preoperative study of the changes in the circulating eosinophils following administration of ACTH or epinephrine will help to predict whether supportive therapy with adrenal cortical hormone is indicated for the operative phase.

SUMMARY

1. Individuals with normal adrenal cortical function show a fall in the number of circulating eosinophils following surgical trauma.

2. The degree of fall is directly related to the length and severity of the trauma. The time interval required for recovery is longer after the more serious procedures.

3. Elderly individuals show a more marked depression and delayed recovery than do young individuals.

4. Pre- and postoperative complications produce and maintain a fall in the circulating eosinophil level.

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IMMEDIATE AND LATE RESULTS OF THE SURGICAL THERAPY OF ACUTE PERFORATED GASTRIC AND DUODENAL ULCER

HENRY W. MAYO, JR., M.D., CHARLESTON, S. C., AND LIEUTENANT (J.G.) CLAIBORNE W. FITCHETT, MEDICAL CORPS, UNITED STATES NAVAL RESERVE

(From the School of Surgery and Gynecology, University of Virginia Department of Medicine, and the University of Virginia Hospital, Charlottesville, Va.)

SURGICAL literature is replete with reports on the results of the surgical therapy of perforated gastric and duodenal ulcer. As DeBakey[6] observed in his monumental review of the subject in 1940, up to that time little diminution had been made in the mortality rate of this disease, despite increased knowledge and improved surgical technique. However, in the last decade, with the introduction of better techniques, increasing interest in and emphasis on preoperative preparation and postoperative management, and with the employment of sulfonamides and antibiotics, the mortality of all surgical disease has shown a marked decline, as has been pointed out by Lehman and Becker (1947).[16]

Statements are frequently found in the older literature to the effect that a perforation of a gastric or duodenal ulcer results in a cure of the disease. There are surprisingly few available reports which concern themselves with the long-term results in patients who have had ulcer perforation closed, and such reports which are available seem to indicate that the aforementioned statements have been made without adequate follow-up data.

In 1946, a follow-up system was inaugurated at the University of Virginia Hospital, an attempt being made to have all patients who had had any kind of surgery for benign ulcer return for examination. Each patient was sent a questionnaire, and attempts were made to trace those who failed to return their questionnaires. All those who answered were requested to come to the follow-up clinic for examination, the plan being to conduct periodic examinations on all of these patients for the duration of their lifetimes, and to institute appropriate medical or surgical therapy when needed. These questionnaires and examinations yielded interesting results. However, it is easy to imagine the almost insuperable difficulties in maintaining a follow-up system from a rural hospital which draws its patients from a radius of several hundred miles, and, consequently, the completeness of the follow-up leaves much to be desired.

Paletta and Hill (1943)[18] reported from this institution a series of 83 operations for acute perforations of gastric or duodenal ulcers, during the period 1925 to 1942, with 14 deaths, a mortality of 16.9 per cent. In the course of the present study, records of 6 other operations were found which chronologically should belong in their report. Thus, the corrected figures for their period of study would be 89 operations with 15 deaths, a mortality of 16.8 per cent.

With these considerations in mind, it was thought worth while to publish a report to indicate the reduction in mortality with the addition of recent surgical adjuvants, and to give an idea of just what happens, over a long period of time, to patients who have had operations for acute perforated gastric and duodenal ulcers. This report includes the series of Paletta and Hill and covers the period from 1925 through December, 1948.

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MATERIAL

During the period of this study, there were 160 operations performed for acute perforations of gastric or duodenal ulcers on 156 patients. Four of these operations represented reperforations in the same patient. Perforations of jejunal or marginal ulcers and chronic perforations of gastric and duodenal ulcers were not included. More than one-half the operations were carried out by the resident surgical staff.

The diagnosis of perforated peptic ulcer is not a difficult one to make clinically, particularly if the history and physical findings are typical; it is not within the province of this paper to discuss the differential diagnosis. As a rule, in this hospital, if the case is a typical one, no time is wasted for the purpose of obtaining films to demonstrate pneumoperitoneum, but if there is a question of diagnosis, these films are obtained. In the present group of 160 cases, only 36 were x-rayed, and 24 of these (66.7 per cent) showed pneumoperitoneum on x-ray examination.

It should be said that a few patients with perforated ulcer, not included in the present group, have been treated in this institution on a conservative regime including intragastric suction, parenteral fluids, transfusions, and antibiotics. These have been patients who were in extremely poor condition at the time of admission, patients in whom the duration of perforation was unusually long and in whom the symptoms appeared to be subsiding, or patients in whom there was considerable doubt as to the diagnosis. However, operative treatment is considered the method of choice when a diagnosis of perforated ulcer is made.

IMMEDIATE RESULTS

In 160 patients operated upon for perforated gastric or duodenal ulcer there were 20 operative deaths, an over-all mortality rate of 12.5 per cent for the 23-year period covered by this study. During the last 10 years (1939 to 1948) there were 9 deaths in a group of 106 cases, a mortality rate of 8.5 per cent, and during the last 5 years (1944 to 1948) there were 2 deaths in a group of 46 cases, a mortality rate of 4.3 per cent. Table I indicates the mortality by years, reflecting the phenomena of reduction in mortality in all surgical disease, previously noted from this institution by Lehman and Becker (1947).[16] Table II is constructed in an attempt to show the influence of various recently introduced surgical aids on the mortality rate in patients operated upon for perforated ulcer. The groups are too small to be of statistical significance, but a trend toward improved mortality is suggested with the use of antibiotics and intragastric suction.[14] A comparison of the University of Virginia Hospital mortality rate with the mortalities in other recently published series is shown in Table III. Fifteen of the 20 deaths were due to peritonitis, 1 due to reperforation and peritonitis, 2 to atelectasis and pneumonia, 1 to anemia, and 1 to "shock."

The various types of operations performed are recorded in Table IV. In general, it has been the policy in this hospital to regard the treatment of perforated ulcer as a lifesaving procedure, but not a curative one, and, as advocated by Graham and Tovee (1945),[11] the simplest type of procedure which

TABLE I. CHRONOLOGICAL TABULATION OF SURGICAL MORTALITY RATE FROM PERFORATED GASTRIC AND DUODENAL ULCERS

YEAR	NUMBER OF CASES	NUMBER OF DEATHS		
1925	2	0		
1926	1	0		
1927	0	0		
1928	2	1		
1929	3	0		
1930	2	0	Mortality	
1931	8	2	1925 through 1938	
1932	6	3	54 Cases, 11 Deaths	
1933	5	0	(20.4%)	
1934	4	2		
1935	4	1		
1936	7	1		
1937	5	0		
1938	5	1		
1939	9	2		
1940	9	1		
1941	17	1		
1942	13	2	Mortality	
1943	12	1	1939 through 1948	
1944	6	0	106 Cases, 9 Deaths	
1945	11	1	(8.5%)	Mortality
1946	9	0		1944 through 1948
1947	13	1		46 Cases, 2 Deaths
1948	7	0		(4.3%)

can cope with the abdominal catastrophe is usually chosen. Consequently, the operative procedure has in most cases been limited to a simple closure of the perforation, most frequently by means of a purse-string suture reinforced with an omental graft.

Bisgard (1945)[5] and Strauss (1944)[21] present cogent arguments in favor of gastric resection in the treatment of early acute perforations, particularly in young individuals in good condition, and their quoted mortality rates lend favor to their thesis. Nevertheless, resection has been performed in only 2 cases in this institution. One, a pylorectomy, was for a posterior wall gastric ulcer with a huge perforation surrounded by a large zone of induration so that closure of the perforation was a technical impossibility. The other was done for a perforated duodenal ulcer of 8 hours' duration with minimal contamination in a man 43 years of age. Both patients survived.

TABLE II. MORTALITY IN RELATION TO SURGICAL ADJUVANTS

GROUP NUMBER	SURGICAL ADJUVANTS	NUMBER OF CASES	NUMBER OF DEATHS	MORTALITY RATE (%)
Group I	No adjuvants	47	11	23.4
Group II	Intragastric suction	30	3	10.0
Group III	Intragastric suction, sulfonamide	46	4	8.7
Group IV	Intragastric suction, penicillin, and sulfonamide	15	1	6.7
Group V	Intragastric suction, penicillin	12	0	0.0
Group VI	Intragastric suction, penicillin, and streptomycin	10	1	10.0

TABLE III. COMPARATIVE MORTALITIES FROM SURGICAL THERAPY OF PERFORATED ULCERS

AUTHOR	NUMBER OF CASES	NUMBER OF DEATHS	MORTALITY RATE (%)
Avent, Patterson, & Chambers (1947)	129	15	11.6
Barber & Madden (1943)	86	11	12.8
Baritell (1947)	88	1	1.1
Berson (1942)	151	23	15.2
DeBakey (1940) (Collected Series)	15,340	3,589	23.4
DeBakey (1940) (Charity Hosp. Series)	209	38	18.2
Donald & Barkett (1946)	116	31	18.5
Estes & Bennett (1944)	80	7	8.7
Forty (1946)	100	17	17.0
Graham (1946)	125	8	6.4
Griswold & Antoncic (1941)	102	20	20.0
Harrison & Cooper (1942)	57	16	28.1
McCarthy & Knoepp (1946)	28	1	3.6
Paletta & Hill (1943)	83	14	16.9
Parker (1941)	52	27	52.0
Shipley & Walker (1949)	188	38	20.0
Timoney (1943)	246	48	19.5
Treiger (1947)	90	24	26.7
Mayo & Fitchett (1950)	160	20	12.5

In the early years of this study, gastroenterostomy in conjunction with closure of the perforation was a popular procedure, since it was feared that closure of a perforated juxtapyloric ulcer would result in pyloric obstruction, but with the introduction of the Wangensteen suction, and the use of the omental graft in closing perforations, this added procedure has fallen from favor, particularly in view of the high mortality rate.

In the group of 160 cases, only 7 females were encountered, and 3 of these died, a mortality rate of 42.9 per cent as compared with the mortality rate of 11.1 per cent in males (Table V). Sixty of the perforations were recorded as being on the gastric side of the pylorus and 100 on the duodenal side. However, in many cases, there was obviously some uncertainty in the operator's mind as to whether the ulcer was duodenal or gastric. Therefore, keeping in mind the known difficulty in identification of location of a perforated "juxtapyloric" ulcer surrounded by inflammatory reaction, the figures concerning location

TABLE IV. ACUTE PERFORATED GASTRIC AND DUODENAL ULCERS

SURGICAL PROCEDURE	TOTAL	DEATHS	MORTALITY (%)
Gastric Ulcers			
Closure perforation	52	8	15.4
Closure perforation, gastroenterostomy	3	2	66.7
Excision and closure perforation	1	1	100.0
Excision and gastroenterostomy	1		
Excision, pyloroplasty	1		
Gastroenterostomy	1		
Gastric resection	1		
Total	60	11	18.33
Duodenal Ulcers			
Closure perforation	73	6	8.2
Excision, pyloroplasty	13		
Closure perforation, gastroenterostomy	9	2	22.2
Pylorectomy	1		
Excision, closure perforation	2		
Excision, pyloroplasty, gastroenterostomy	1	1	100.0
Closure perforation, pyloroplasty	1		
Total	100	9	9

should not be regarded as absolute, but are interesting in that they indicate a mortality rate for perforated gastric ulcer more than twice the rate for perforated duodenal ulcer (Table V). Paletta and Hill (1943)[18] reviewed reports of 9 other authors showing an average mortality of 33.2 per cent for patients with gastric ulcers and 21.6 per cent for those with duodenal ulcers.

The average age of all patients in the series was 40.9 years. The average age of the surviving patients was 39.8 years, while the average age of the patients not surviving was 48.9 years. The average duration of the symptoms

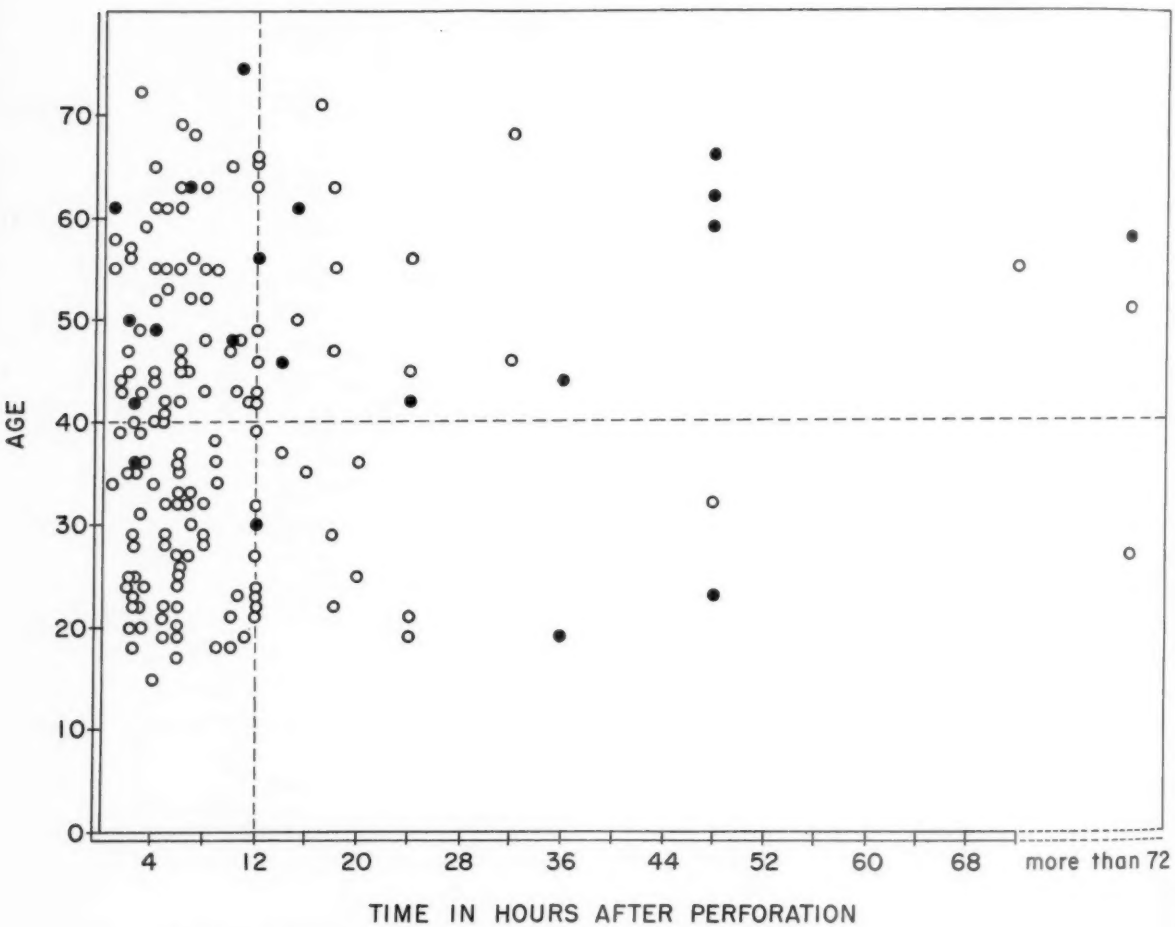

Fig. 1.—Scattergram indicating relationship of mortality rate to age of patient and time elapsing between perforation and operation. Circles indicate survivals and dots indicate deaths.

of perforation in the entire series, excluding one patient whose history was entirely unreliable, was 10.2 hours, while the average duration of the symptoms of perforation in the patients not surviving was 20.4 hours, and in the surviving patients 8.8 hours. Fig. 1 shows the comparatively high mortality rate which occurs in the patients in whom considerable time has elapsed after perforation before surgery is performed, and also represents the age distribution of this series of cases, indicating a higher mortality in the older groups.

Twenty-four (15 per cent) of the patients in the group had had no definite ulcer symptoms prior to perforation. The mortality rate was higher in this

TABLE V. MORTALITY RATES

	NUMBER OF CASES	DEATHS	MORTALITY RATE (%)
	Mortality Rate in Relation to Sex		
Male	153	17	11.1
Female	7	3	42.9
	Mortality Rate in Relation to Location of Ulcer		
Gastric	60	11	18.3
Duodenal	100	9	9.0

group (25 per cent) than in any other, and next highest in those who had had symptoms more than 10 years (Table VI).

TABLE VI. MORTALITY RATE IN RELATION TO DURATION OF SYMPTOMS PRIOR TO PERFORATION

DURATION OF SYMPTOMS	NUMBER OF CASES	PER CENT OF TOTAL	NUMBER OF DEATHS	MORTALITY RATE (%)
No past symptoms	24	15	6	25.0
0 to 6 months	32	20	2	6.2
6 to 12 months	17	10.6	0	0.0
1 to 5 years	36	22.5	5	13.9
6 to 10 years	14	8.7	0	0.0
More than 10 years	35	21.8	7	20.0

LATE RESULTS

Patients followed less than 6 months were considered to be incompletely followed. Obviously, 6 months' follow-up does not constitute a complete follow-up since several reports[2, 13, 14, 19] indicate that following a closure of a perforated ulcer, there is often a temporary amelioration of symptoms, with return of ulcer activity and symptoms months or years later. However, for purposes of this study, all those individuals who were followed more than 6 months, by questionnaire, examination, or both, were assigned to the group "completely followed." The length of follow-up in these cases varied between 6 months and 25 years, with an average length of 5.8 years follow-up. All except 18 of these patients were followed more than 1 year.

Ninety-two (or 65 per cent of the 140 surviving patients) were followed "completely," while 7 had an incomplete follow-up and 41 were not followed at all (Table VII). Of the 92 patients completely followed, only 20 (14.3 per cent) were free of symptoms when last seen. Of these 20 patients, 9 had gastric perforations and 11 duodenal. Seventeen, or 12.2 per cent, had moderate dyspeptic symptoms, and 21, or 15.0 per cent, had definite ulcer activity and rather severe symptoms. Forty-two of the patients (30.0 per cent) were main-

TABLE VII. FOLLOW-UP DATA ON 140 NONFATAL CASES OF PERFORATED ULCER

	SYMPTOMS				ON			
FOLLOW-UP	SYMPTOM-FREE	MILD	MODERATE	SEVERE	MEDICAL THERAPY	FURTHER SURGERY	TOTAL CASES	PER CENT OF SURVIVORS
Complete	20 (14.3%)*	17 (12.2%)	21 (15.0%)	34 (24.3%)	42 (30.0%)	23 (16.4%)	92	65.7
Incomplete	2 (1.4%)	3 (2.2%)	1 (0.7%)	0 0	3 (2.2%)	0 0	7	5.0
None							41	29.3
Total	22 (15.7%)	20 (14.4%)	22 (15.7%)	34 (24.3%)	45 (32.2%)	23 (16.4%)	140	100

*Percentages refer to number of cases followed.

tained fairly well with medical therapy. Twenty-three (16.4 per cent) patients on whom follow-up study was done had symptoms sufficiently severe to require further surgical procedures at a later date, the interval between operations varying between 5 days and 12 years.* It is interesting that 6 patients had a second perforation, 1 subsequent to the termination of this study, and 1 (gastric) 5 days subsequent to the closure of a perforated duodenal ulcer. The types of operations performed are tabulated in Table VIII.

TABLE VIII. FOLLOW-UP DATA ON PERFORATED ULCERS; SURGICAL PROCEDURES PERFORMED ON 23 PATIENTS SURVIVING INITIAL PERFORATION

Subtotal gastrectomy	12
Gastroenterostomy	2
Vagotomy, transthoracic	1
Vagotomy and subtotal gastrectomy	1
"Jejunal patch" operation	1
Pylorectomy	1
Closure of perforation	5

DISCUSSION

It has been previously recorded by numerous authors[1, 2, 6, 11, 12, 13, 18] that the mortality rate resulting from operations on perforated peptic ulcer varies directly with the age of the patient and the duration of the symptoms of perforation. These observations have been confirmed in this study (Fig. 1). The results of the study also seem to indicate that perforated gastric ulcer is a much more serious disease (Table V) than perforated duodenal ulcer as previously recorded by DeBakey (1940)[6] and others, and much more serious in women than in men. The mortality rate was higher in those patients who had had no previous ulcer symptoms and in those patients who had had symptoms for a great many years, than in those patients who had had symptoms for a moderate number of years (Table VI). Simple closure of the perforation seems to carry with it a relatively low mortality, and the addition of a gastroenterostomy has in this series raised the mortality rate to a prohibitive figure. This adds some justification to the viewpoint that the simplest type of procedure possible is the most desirable in catastrophes of this kind. The influence of antibiotics and other surgical adjuvants may have materially decreased the mortality rate.

The follow-up records seem to refute the old idea that perforation of an ulcer results in a cure of the disease, since only 14.3 per cent of the patients on whom follow-up studies were done remained free of symptoms, 30.0 per cent of these had symptoms so severe as to require medical therapy, and 16.4 per cent had symptoms or complications sufficiently severe to require further surgery.

SUMMARY

A study of 160 cases of perforated gastric and duodenal ulcers operated upon from 1925 to 1948 at the University of Virginia Hospital has been presented, indicating 20 operative deaths, an over-all mortality rate of 12.5 per cent. In the last five years of the study this rate was reduced to 4.3

*Since this paper was submitted for publication, one of the patients classified as being "maintained on medical therapy" had a subtotal gastrectomy performed because of uncontrollable symptoms.

per cent, concomitant with the increasing use of antibiotics and other surgical adjuvants. The direct influence of the age of the patient and the duration of symptoms of perforation on the mortality rate has been noted. Follow-up records on 92 of the surviving patients seem to indicate that a patient is rarely cured of the ulcer diathesis following closure of a perforated ulcer.

CONCLUSIONS

1. The operative mortality rate of patients with perforated gastric and duodenal ulcer has been progressively reduced during the past 23 years.

2. Simple closure of the perforation is the treatment of choice for perforated gastric and duodenal ulcers, although gastrectomy might be considered in the occasional case with minimal contamination.

3. Patients who have had perforated gastric or duodenal ulcers should be considered as "ulcer cases" and should be under medical supervision for a long period of time.

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ACUTE INTESTINAL OBSTRUCTION

Comparative Studies of Small Intestinal and Colic Obstruction

Marshall L. Michel, Jr., M.D.,* Leonard Knapp, M.D.,* and
Arthur Davidson, M.D., New Orleans, La.

INTRODUCTION

WITHIN the last decade, numerous advances have improved the results and increased the extent of elective gastrointestinal surgical procedures. Increased knowledge of the physiology of the intestine, chemotherapy, antibiotics, intestinal intubation, better anesthesia, refinements in surgical technique, and other advances are responsible for these improvements.

However, recent reports on acute intestinal obstruction reveal that the results in this type of case are not commensurate with the improvements in elective gastrointestinal surgery. Eliason and Welty[1] recently reported an 8 per cent mortality in patients with small intestinal obstructions and a 16 per cent mortality in those with acute obstructions of the colon. Calihan, Kennedy, and Blain[2] reported a 20 per cent mortality with small intestinal obstruction. Brindley[3] reported a 21 per cent mortality with colon obstruction.

We have recently analyzed 258 cases of acute intestinal obstruction of both the small and large intestine; these patients have been treated on all services at Charity Hospital and Touro Infirmary in New Orleans, La. These studies reveal a mortality of 16 per cent with small intestinal obstruction, and 30 per cent with acute obstruction of the colon.

In view of this prevalent high mortality, it is evident that acute intestinal obstruction remains one of the serious problems in abdominal surgery, and further study of the subject, including both the clinical and experimental aspects, is indicated.

CLASSIFICATION

Mechanical obstruction of the intestinal tract (mechanical or dynamic ileus) has been classified in several different ways. The most popular classification is into high and low obstructions (Treves).[4] Some authors have rightly emphasized the differences between acute and chronic obstructions.

It is our opinion, based largely on the case analyses which we have made, that the most important and valuable way of classifying mechanical ileus is to distinguish between small intestinal obstructions and obstructions of the colon. Such a classification has been suggested, both directly and indirectly, by previous writers. However, it is our impression, from perusing the literature, that the differences between small intestinal obstructions and obstructions of the colon have not been sufficiently emphasized.

In fact, these two types of intestinal obstruction differ in so many respects that we believe obstructions of the small intestine and obstructions of the colon should probably be discussed as two entirely different subjects.

Appreciation of the fact that an intestinal obstruction may be either acute or chronic is also important. Both small intestinal and colic obstructions can

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*From the Department of Surgery, Tulane University School of Medicine.

be either acute or chronic. However, here, as in many other categories, there is a difference between colic and small bowel obstruction.

Chronic obstruction of the colon is relatively common, whereas chronic obstruction of the small intestine is relatively uncommon.

This presentation will deal primarily with acute obstructions of both the colon and small intestine. Classification of intestinal obstruction into the small intestinal and colic groups is not infallible. In some respects, colic and small intestinal obstructions overlap and there are some definite similarities. However, the dissimilarities far outnumber the similarities.

ETIOLOGY

Entirely different etiological factors usually produce acute small bowel obstruction as compared to the factors which produce acute obstruction of the colon (Fig. 1).

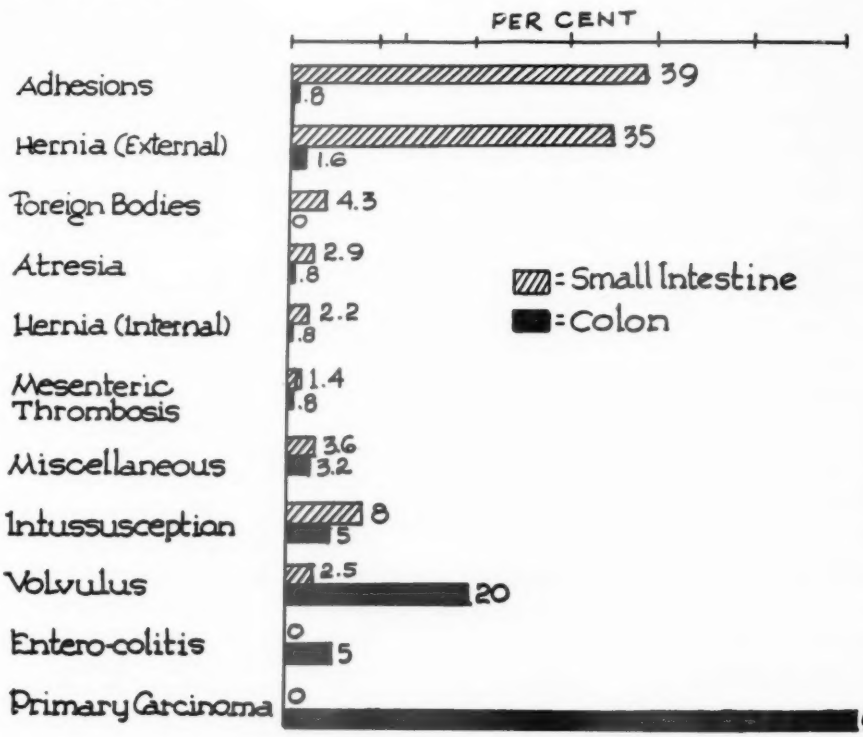

Fig. 1.—Etiology in 258 cases of acute intestinal obstruction.

Postoperative adhesions and hernias are the most common causes of obstruction of the small intestine. However, these two conditions rarely produce acute obstruction of the colon.

In this series, adhesions produced 39 per cent of the obstructions of the small intestine, whereas incarcerated or strangulated external abdominal hernias produced 35 per cent of the obstructions. The supersedence of adhesions over external hernias as the most common cause of small bowel obstruction is becoming more evident in recent studies.

In most textbooks and older writings, hernia is usually considered to be the most common cause of small bowel obstruction. However, postoperative adhesions are now the most frequent cause of this type of obstruction.

There are three reasons for this change: (1) An increased number of abdominal operations are now being performed (particularly gynecologic procedures); (2) the lay public is becoming increasingly conscious of the dangers of complicated hernias, as well as becoming aware of the lack of seriousness of elective herniorrhaphy; (3) many industries will not accept workers who have hernias, thereby forcing them to have elective operations.

Acute colic obstruction, on the other hand, is most often produced by primary carcinoma of the colon. This was so in 62 per cent of the cases which we studied. Wangensteen[5] and others have found that primary carcinoma is the cause of colic obstruction in as high as 90 per cent of the cases.

Primary carcinoma of the small intestine does occur. However, it is a rare cause of acute small bowel obstruction and was not found to be present in any case in this series.

Volvulus of the colon is the second most common cause of acute colic obstruction, and accounted for 20 per cent of our cases. Volvulus does involve the small intestine, but is relatively uncommon. Furthermore, primary volvulus of the small intestine, that is volvulus which is not precipitated by fixation of part of the bowel by postoperative adhesions, is an extremely uncommon form of acute small bowel obstruction.

Inflammatory conditions of the intestine, particularly diverticulitis, are an occasional cause of acute colic obstruction. This was found in 5 per cent of the cases in this series.

On the other hand, although inflammatory conditions of the small intestine do occur (Crohn's disease, and others), they practically never manifest themselves as an acute small bowel obstruction. Inflammatory changes in the wall of the small bowel were not found to be the cause of the obstruction in any case in this series.

Intussusception may occur as the cause of either colic or small intestinal obstruction. There is a definite etiological overlapping between colic and small intestinal obstructions in this category. In our series, 8 per cent of the small bowel obstructions and 5 per cent of the large bowel obstructions were due to intussusception.

Mesenteric thrombosis is more common in the small intestine than it is in the colon (Fig. 1). There was only one case of acute colic obstruction which was the result of primary thrombosis of the mesocolic vessels.

Internal hernia is a more common cause of obstruction of the small intestine than of the colon (Fig. 1). There was only one obstruction of the colon in this series that was produced by an internal hernia.

Atresia of the intestinal tract is more common in the small intestine than it is in the colon. When it does occur in the colon, it usually is coincidental with a small bowel atresia and the clinical manifestations are those of small bowel obstruction and not of large bowel obstruction.

As might be expected, foreign bodies (such as gallstones), which cause intestinal obstruction, practically always lodge in the small intestine and rarely obstruct the colon. This obstruction usually occurs in the terminal ileum, which is the narrowest part of the small intestine. If a foreign body is able to traverse the entire small intestine it will probably not become lodged in the large intestine. In our series, 4.3 per cent of small intestinal obstructions were due to foreign bodies, and there were no obstructions of the colon due to this cause.

It is evident from this analysis, therefore, that entirely different etiological factors are usually responsible for small intestinal obstructions, as compared to those which cause acute colic obstruction.

AGE

Generally speaking, colic obstructions usually occur in an older age group than do small intestinal obstructions. This is particularly true of the common causes of colic obstruction (carcinoma, diverticulitis, and volvulus).

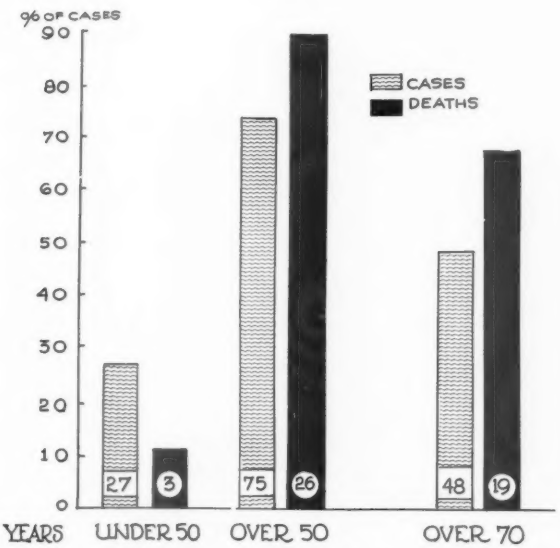

Fig. 2.—Distribution of cases and deaths in relation to surgical risk in 103 cases of obstruction of the large bowel. (From Marshall L. Michel, Jr., and Emit L. McCafferty, Arch. Surg. 1948[6])

In this series, the average age of the patients with colon obstructions was 51 years as compared to an average age of 40 years in those with the small intestinal obstructions. That age is a factor in the mortality is evident from the fact that in the fatal cases the average age of patients with colon obstructions was 59, and that of the group with small intestinal obstruction was 45.

In a previous analysis of common colon obstructions,[6] it was found that 90 per cent of the fatalities occurred in people over 50 years of age, and 48 per cent occurred in patients over 70 years of age (Fig. 2).

INCIDENCE

Acute obstruction of the small intestine is more common than acute obstruction of the colon. Between Jan. 1, 1944, and Dec. 31, 1946, there were

admitted to Charity Hospital in New Orleans 486 patients with small intestinal obstruction, and 94 patients with colon obstruction. Small intestinal obstruction, therefore, is approximately five to six times more common than acute obstruction of the colon in this institution.

LOCATION OF THE OBSTRUCTION

Both acute obstruction of the colon and acute obstruction of the small intestine show a definite predilection for particular parts of the intestinal tract.

Acute obstructions of the small intestine are more common in the middle and terminal ileum. There are several reasons for this. The terminal ileum is the most movable part of the small intestine and is also the part which has the smallest lumen. It is nearest to the site of the most common abdominal operations (appendectomy, gynecologic procedures, and hernioplasty) and is thereby more likely to become involved in postoperative adhesions. Also, the terminal ileum is nearest to the location of the common external abdominal hernias (inguinal, femoral, and ventral), which might produce incarceration or strangulation of an involved part of the small intestine. Furthermore, it is the terminal ileum which most often becomes intussusceipted into the cecum in the common type of intussusception.

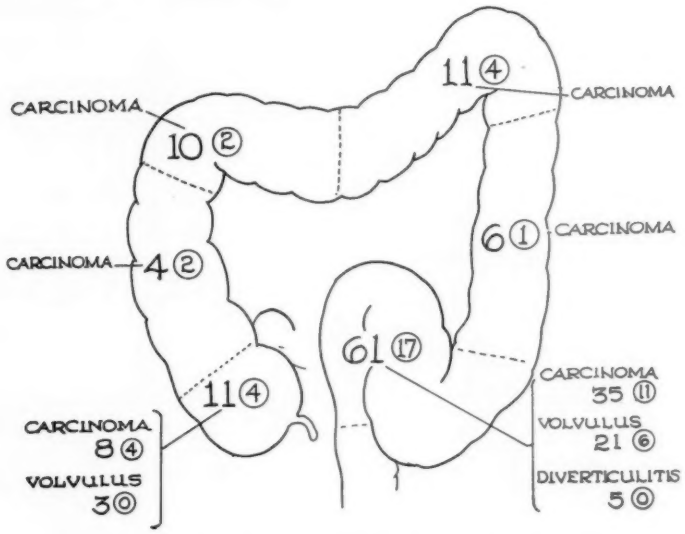

Fig. 3.—Regional distribution in 103 cases (including 30 deaths) of acute obstructions of the large bowel. (From Marshall L. Michel, Jr., and Emit L. McCafferty. Arch. Surg. 1948.[6])

Acute colic obstruction, on the other hand, shows a definite predilection to involve the sigmoid colon.

Fig. 3 illustrates the location of 103 acute obstructions of the large bowel produced by the common causes of colic obstruction. The predominance of obstructions of the colon occurring in the sigmoid is evident.

There are several reasons why acute malignant obstruction of the colon is most common in the sigmoid and left colon. The lumen of the left colon is smaller and the walls are thicker and less distensible. The fecal contents are more solid than those of the right and transverse colons and thereby contribute

another obstructive factor. A carcinoma in the left colon is readily traumatized by the solid feces, with resulting ulceration, infection, edema, and swelling. The annular, "napkin ring" type of carcinoma is more common in the sigmoid and left colon.

The occurrence of volvulus of the colon implies excessive mobility of the affected part of the bowel and is the result of (1) a long and freely movable intestinal mesentery, (2) a relatively short mesenteric root, (3) proximity of intestinal loops in relation to the points of fixation, or (4) an increase in the length of the intestinal loop.[6] Volvulus of the colon in our series was most common in the sigmoid, which more often fulfills the foregoing requirements than does any other part of the colon.

There were three cases of acute volvulus of the cecum in this series. This condition usually occurs in younger individuals and is the result of abnormal mobility of the ileocecal region and right colon. Also, cecal volvulus does not show the predilection for the male sex as does sigmoid volvulus.

Although diverticuli can occur in any part of the colon, diverticulitis is much more common in the sigmoid colon than elsewhere. Acute colic obstruction due to diverticulitis occurs practically always in the sigmoid, as is shown in this series and other studies. Some of the factors, which make acute malignant obstruction in this region more common, again enter into the picture. The small lumen of the sigmoid, the thick and comparatively rigid walls, and the solid fecal strain all play a part in the obstruction caused by diverticulitis.

PHYSIOLOGY AND PATHOLOGY

The physiologic and pathologic changes in acute obstruction of the small intestine differ from those in acute obstruction of the colon.

In acute obstruction of the small intestine, the intestine above the site of the obstruction becomes progressively more and more distended with fluid and gas in direct proportion to the length of time since the onset of the obstruction. This distention is most marked immediately above the site of the obstruction and will eventually involve the entire proximal intestinal tract, unless the obstruction is released.

As a result of the distention, there are edema, ulceration, inflammatory changes, and ischemia of the bowel wall above the site of obstruction. "Weeping" of the mucosa takes place.

Large amounts of fluid, which closely resemble blood plasma, escape directly into the lumen of the intestinal tract. As a result of this fluid loss, severe chemical changes take place in the fluids and tissues of the body. The end results are dehydration, hypochloremia, alkalosis or acidosis, hypoproteinemia, hypovitaminosis, hemoconcentration, and azotemia.

Acute colic obstruction, on the other hand, rarely produces the picture of marked chemical imbalance which is so characteristic of small intestinal obstruction. In many cases of colic obstruction, as a result of competency of the ileocecal valve, the obstruction is of the closed loop type; that is, the obstructing lesion, usually a carcinoma, produces a distal obstructing point and the competent valve produces the proximal obstructing point (Wangensteen). This type

of obstruction occurs most commonly as the result of an annular carcinoma of the left colon (Fig. 4). Therefore, the distention in acute colic obstruction is often limited to a closed loop of colon, and there is little or no concurrent distention of the small intestine, particularly in the early stages of the obstruction.

A large amount of fluid and gas accumulates in the colon. However, due to the fact that the ileus is unable to "back up," the degree of distention in the closed loop of colon is very marked. Extensive inflammatory changes, edema, ulceration, and areas of focal necrosis occur. As a result, there is danger of perforation of the colon if the obstruction is not relieved. This perforation usually occurs in the cecum, which is the thinnest and most distensible part of the large intestine.

The patient with untreated acute obstruction of the colon will usually, therefore, succumb to perforation and peritonitis, whereas the patient with untreated acute small bowel obstruction will frequently die as a result of severe chemical changes.

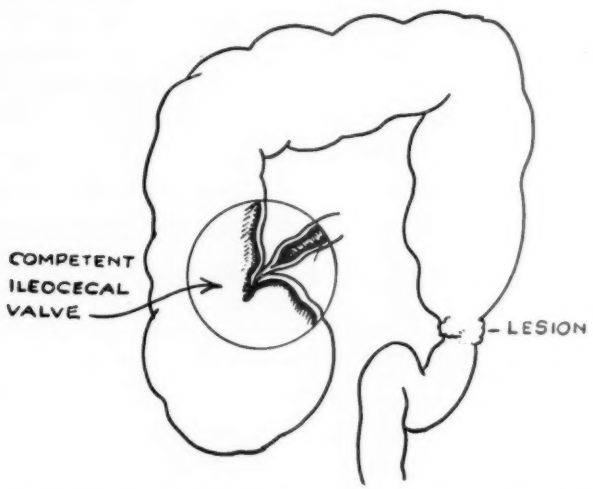

Fig. 4.—Closed loop obstruction of the colon due to annular carcinoma of left colon.

Strangulation is a serious pathologic change which can occur in any type of acute mechanical obstruction. Gross strangulation is more common in obstruction of the small intestine than it is in obstruction of the colon. In our series of 138 cases of small intestinal obstruction, there were twenty-four with gangrene (18 per cent). In 120 cases of acute colic obstruction, there were only six instances of gangrene (5 per cent).

When gangrene occurs, the mortality is markedly increased, whether the obstruction is in the small intestine or in the colon. In our series of small intestinal obstructions, there was a 46 per cent mortality in those patients with gangrene as compared to a 16 per cent over-all mortality. In the colic obstructions, there was a 50 per cent mortality in the patients with gangrene as compared to an over-all 30 per cent mortality.

The occurrence of gangrene in an acute intestinal obstruction does not necessarily depend upon the duration of the obstruction. Strangulation may occur relatively early in the course of the disease. Its occurrence depends

largely on mechanical and pathologic factors resulting from certain etiological types of obstruction rather than on the duration of the obstruction. At Johns Hopkins Hospital,[2] in 204 cases of small intestinal obstruction, the patients without gangrene had been sick fifty-eight hours when operated upon, and the patients with gangrene had been sick only fifty hours prior to operation.

In small intestinal obstruction, gangrene is usually the result of internal or external hernias, volvulus, or mesenteric thrombosis. In colic obstructions, gangrene is most often produced by volvulus. Spontaneous mesocolic thrombosis, as previously mentioned, is a relatively rare condition as compared to mesenteric thrombosis of the small intestine.

CLINICAL PICTURE

As a result of the previously mentioned differences between small intestinal and colic obstructions, it follows that the clinical picture in the majority of cases differs also.

If a detailed history is possible, it is frequently found that the patient with acute colic obstruction gives a history of having had previous mild attacks suggestive of incomplete obstruction. This is particularly true in cases with carcinoma or diverticulitis and was also found in an appreciable number of the volvulus cases.

On the other hand, relatively few of the patients with small intestinal obstructions gave histories of previous similar attacks.

The majority of obstructions in the colon have an insidious onset. This, again, is usually the case in carcinoma and diverticulitis obstructions, whereas volvulus and intussusception usually have an abrupt onset.

In small intestinal obstruction, on the other hand, the onset is almost always acute and violent.

As a result of the insidious onset of colon obstructions, the actual duration of these obstructions when first seen is usually longer than the duration of small intestinal obstructions.

Characteristically, the abdomen of the patient with a colon obstruction is more markedly distended than the abdomen in most small intestinal obstruction cases, except in far-advanced, low, small bowel obstruction.

The colon obstructions are clinically very distended in spite of the fact that in many cases the distention is limited to a closed loop of colon.

It must be remembered, however, that some cases of colic obstruction, particularly those due to carcinoma of the right colon, may manifest only slight clinical distention.

Nausea and vomiting are considered to be classical symptoms of acute mechanical obstruction of the intestinal tract. However, nausea and vomiting are frequently absent in colon obstruction, as was found in 17.5 per cent of the colon obstructions in the present series. This absence of nausea and vomiting is particularly common in the closed-loop carcinoma obstruction. In a previous series[8] of acute malignant obstructions, nausea and vomiting were absent in 22 per cent of such cases.

On the other hand, nausea and vomiting are almost always present in small intestinal obstruction. In this series they were absent in only three cases (2.2 per cent). Two of the three patients were moribund when admitted to the hospital, and it is not at all certain that nausea or vomiting or both had not been present previous to admission to the hospital.

It must be emphasized at this point, that in low small intestinal obstruction the onset of nausea and vomiting may not occur until relatively late in the disease.

That a patient with an acute intestinal obstruction may defecate or expel flatus after the onset of the obstruction is not as generally appreciated as it should be. This paradoxical phenomenon, in our experience, occurred more frequently in small intestinal obstruction than in colon obstruction. In 27.7 per cent of the small intestinal obstructions and in 17.5 per cent of the colon obstructions, the patient either defecated or expelled flatus after the onset of the obstruction.

Abdominal tenderness is not considered a classical finding in acute intestinal obstruction. However, this physical sign may be present in some cases of acute intestinal obstruction. Abdominal tenderness is more common in patients with acute colic obstruction than it is in those with an acute small intestinal obstruction.

Localized abdominal tenderness in acute colic obstruction may be found over a markedly distended cecum as a result of a closed-loop obstruction anywhere in the colon. This phenomenon resulted in a mistaken diagnosis of acute appendicitis in three cases of acute malignant obstruction of the left colon in this series.

Furthermore, in colon obstruction there may be marked tenderness directly over an obstructing carcinoma or over an area of diverticulitis.

Volvulus of the colon is often accompanied by abdominal tenderness directly over the twisted loop of bowel due to the associated circulatory disturbances.

On the other hand, abdominal tenderness in small intestinal obstruction is relatively uncommon except when strangulation occurs.

The presence of a palpable tender mass in an acute small bowel obstruction practically always means strangulation, but, as stated previously, these findings may be present in colic obstruction without gross gangrene.

It is appropriate at this time to mention other signs of gangrene in intestinal obstruction. The pain changes from a colicky to a constant type. Circulatory collapse may be profound. The total white blood count is often markedly elevated with a high percentage of polymorphonuclear leucocytes.

LABORATORY FINDINGS

The laboratory findings in acute small intestinal obstruction differ from those found in acute colic obstruction, and are the result of different physiologic disturbances. The changes which are manifest in small intestinal obstruction are the result of the acute obstruction, whereas those changes found in colic obstruction are most often the result of long-standing disease, such as carcinoma or diverticulitis.

The total red blood cell count and hematocrit may be increased in small intestinal obstruction. In many advanced cases of lower small bowel obstruction, the degree of hemoconcentration is marked and is a serious physiologic disturbance which must be actively combated.

On the other hand, in many cases of colon obstruction, a definite degree of anemia is found. This is not due to the obstruction per se, but is the result of long-standing disease (carcinoma or diverticulitis).

It is uncommon to find leucocytosis in patients with small intestinal obstruction except in those instances in which strangulation has occurred or in which peritonitis is also present. On the other hand, moderate degrees of leucocytosis with an increased polymorphonuclear count are relatively common in the patients with colon obstruction. This is probably the result of the extensive inflammatory changes which occur in the colon proximal to the obstructing lesion, particularly in the closed-loop obstructions.

The blood chlorides are frequently decreased in small intestinal obstruction. Chloride deficiencies were found in none of the acute cases of colic obstructions which we analyzed.

Serum protein deficiencies were manifest in a large percentage of cases of both small intestinal and colon obstructions in this series. However, the cause of this phenomenon differs in the two types of obstruction.

The lowered serum protein found with small intestinal obstruction is due to the transudation of a large amount of protein-containing fluid into the lumen of the small bowel. On the other hand, the serum protein deficiency found with colon obstruction is usually the result of long-standing disease, particularly carcinoma.

Varying degrees of azotemia, as manifest by an increased nonprotein nitrogen, are frequently present with small intestinal obstructions, particularly in far-advanced cases. Such a finding was almost entirely absent in cases of acute colon obstructions.

As mentioned previously, alkalosis and acidosis may occur in cases with small bowel obstruction as the result of extensive loss of fluid into the lumen of the small intestine. Such changes are practically never seen with acute colon obstructions.

X-RAY FINDINGS

X-ray studies of the abdomen in acute intestinal obstruction are important from a diagnostic standpoint. Correct interpretation of the x-ray picture will frequently differentiate between colic and small intestinal obstructions. This diagnostic differentiation is of importance in the correct handling of all cases of mechanical ileus.

The surgeon and the radiologist must not be content with a nonspecific diagnosis of "intestinal obstruction." The films must be studied closely. The distended loops of bowel can usually be definitely identified in order to localize the site of obstruction. Wangensteen[5] has emphasized repeatedly the importance of careful attention to the details of the scout film of the abdomen in acute ileus.

The scout films should be taken in both the erect and supine positions in order to demonstrate the degree of distention and the presence of fluid levels.

In early stages of obstruction, the scout film may not be definitely diagnostic. A series of films taken at regular intervals of one to several hours will in some cases eventually lead to a definite diagnosis.

On the other hand, it must be remembered that strangulation in small intestinal obstruction may occur early in the disease and that delay may be hazardous. Although the blood supply is compromised, the lumen of the bowel may not be completely occluded and there will be little or no ileus manifest on the scout film.

Fig. 5 demonstrates the scout film of a patient who had eighteen inches of gangrenous small intestine due to a strangulated hernia at the site of a Baldy-Webster uterine suspension. There was almost no distention of the small intestine manifest on the scout film.

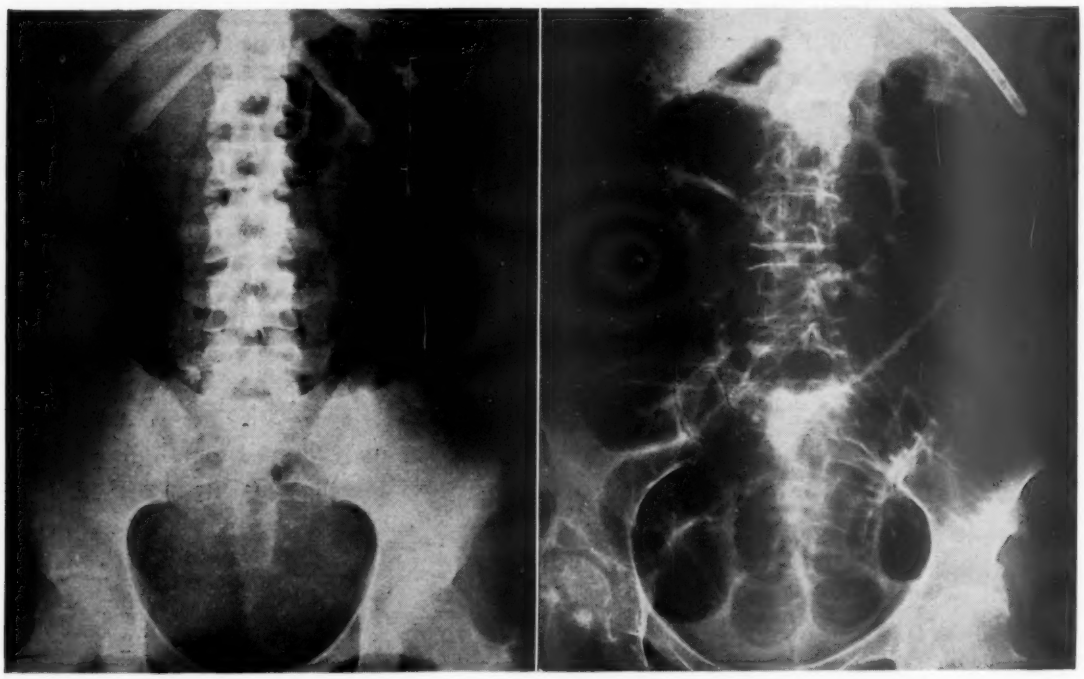

Fig. 5. Fig. 6.

Fig. 5.—Gangrenous obstruction of ileum without demonstrable distention.
Fig. 6.—Advanced ileal obstruction with marked distention.

On the other hand, Fig. 6 shows a typical well-advanced lower small bowel obstruction with marked distention of practically the entire intestine above the site of obstruction. The coarse mucosal folds shown by the jejunal loops can be easily compared to the relatively smooth outline of the distended loops of ileum.

The typical closed-loop colon obstruction often presents a classical x-ray picture, as demonstrated in Fig. 7. In this instance the obstruction was due to a carcinoma of the midsigmoid and the scout film shows the distention to be limited entirely to the colon, indicating complete competency of the ileocecal valve.

Volvulus of the colon will often also manifest itself as a closed loop of distended colon, as is shown in Fig. 8. In this case, there is a markedly distended loop of colon lying transversely in the abdomen with little or no distention of

Fig. 7.—Closed loop obstruction due to carcinoma of sigmoid colon.

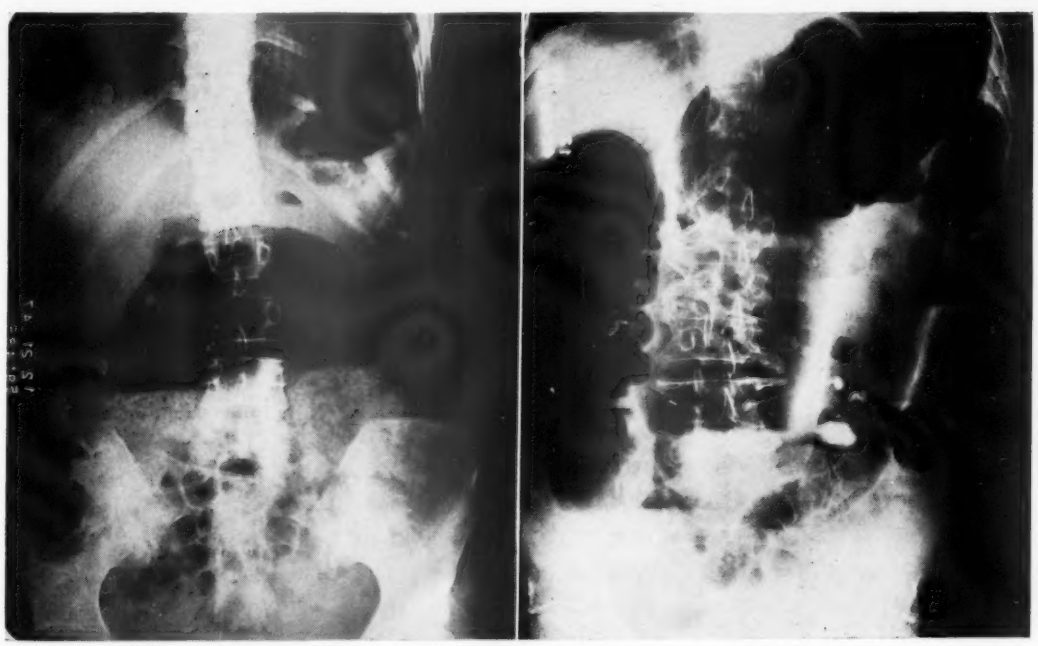

Fig. 8. Fig. 9.

Fig. 8.—Acute volvulus of the right colon. (From Marshall L. Michel, Jr., and Emit L. McCafferty, South. Surgeon 1948.[11])

Fig. 9.—Acute volvulus of the sigmoid colon. (From Marshall L. Michel, Jr., and Emit L. McCafferty, South. Surgeon 1948.[11])

the remaining parts of the intestinal tract. The obstruction was the result of an acute volvulus of the right colon, which assumed a transverse position in the abdomen.

Volvulus of the sigmoid colon is the most common type of colic volvulus and is usually readily diagnosed by the scout film. Fig. 9 shows a markedly distended sigmoid loop extending high up to the diaphragm on the left. The conical termination of the gas column inferiorly is typical.[10] This is a relatively far-advanced case. Proximal distention of the right colon and small intestine are beginning to take place.

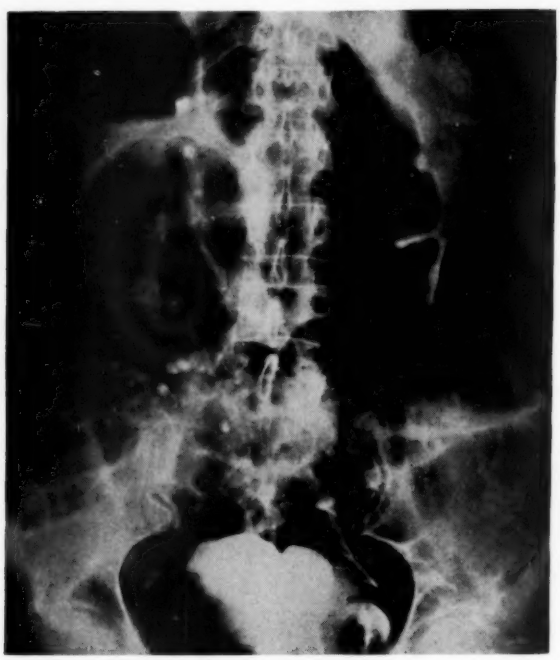

Fig. 10.

Fig. 11.

Fig. 10.—Abrupt termination of barium enema caused by carcinoma.
Fig. 11.—Conical termination of barium enema in sigmoid volvulus. (From Marshall L. Michel, Jr., and Emit L. McCafferty, South. Surgeon 1948.[11])

It must be remembered, however, that the scout film is not always absolutely diagnostic. This is particularly true in the patient who is markedly distended. In such cases it is often difficult to determine whether or not one is dealing with a mechanical or paralytic ileus and whether or not the obstruction is in the colon or in the lower small intestine.

Whenever an intestinal obstruction is suspected, it is our opinion that the barium enema can be an important diagnostic aid in many cases. On the other hand, Wangensteen[5] and Dennis[9] do not believe that the barium enema should be used in these acute cases because of the danger of perforation of the colon. However, if the enema is given with care, there is, in our opinion, no real danger of perforation. A colic obstruction can be definitely localized thereby, and frequently the etiology can be determined.

Fig. 10 shows the abrupt termination of the barium column caused by a rectosigmoid carcinoma. In this case, there was marked generalized distention

of both the small and large intestine. Fig. 11 shows the typical conical termination of the barium column produced by a sigmoid volvulus.

In over 90 per cent of the patients with acute colic obstruction in this series in whom the barium enema was used, it was possible to make an exact etiological diagnosis, in addition to being able to localize the exact site of the obstruction. There were no incidences of perforation of the colon as a result of the barium enema.

On the other hand, it must be emphasized that barium must never be given by mouth in any type of acute intestinal obstruction, whether it is in the small intestine or colon.

SURGICAL RISK

The role of the general condition of the patient as evaluated from the standpoint of surgical risk is of importance in dealing with any type of acute intestinal obstruction.

In analyzing these cases we found that acute colic obstructions are, generally speaking, poorer risks than the small intestinal obstructions.

In previously analyzing 103 cases of acute colic obstruction[6] due to the common causes (volvulus, diverticulitis, and carcinoma), it was found that 41 per cent of the patients were classified as good surgical risks, 45 per cent as fair surgical risks, and 17 per cent as poor surgical risks. The mortality rate, as is shown in Fig. 12, demonstrates the high mortality in the poor-risk patients.

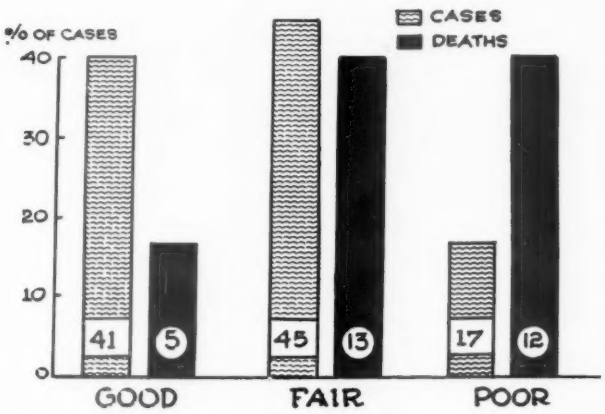

Fig. 12.—Distribution of cases and deaths in relation to surgical risk in 103 cases of acute obstruction of the colon. (From Marshall L. Michel, Jr., and Emit L. McCafferty, Arch. Surg. 1948.[6])

On the other hand, in the small intestinal obstructions in this series, only four cases (3.4 per cent) of the entire group were classified as poor surgical risks, forty-three cases (37.1 per cent) were classified as fair surgical risks, and sixty-nine cases (59.5 per cent) were classified as good surgical risks. The mortality was again definitely affected by the general condition of the patient.

The treatment in any particular case of intestinal obstruction is necessarily influenced by the general condition of the patient, as evidenced by this study.

In acute colic obstructions, the poor condition of many patients is one factor which limits the extent of the surgical procedure. Direct attack upon

the obstructing lesion is usually not indicated, and decompression of the proximal colon is the procedure of choice.

TREATMENT

As a result of the numerous differences between small intestinal obstruction and colic obstruction, which have been enumerated, it naturally follows that the treatment of the two types of obstruction also differs in many respects. Generally speaking, most acute obstructions of the small intestine should be treated by direct surgical attack upon the lesion. At the same time that the obstruction is relieved, the cause of the obstruction is also remedied.

On the other hand, colic obstruction, particularly when due to carcinoma or diverticulitis, is treated by indirect surgical attack. The colon proximal to the lesion is decompressed and no attempt is made to remove the obstructing lesion at the primary operation. The cause of the obstruction is subsequently eradicated at a second operative procedure.

Small Intestine.—The treatment of small intestinal obstruction should be directed toward three objectives: (1) early operative release of the obstruction; (2) the replacement of fluid, hemic, and vitamin deficiencies; and (3) decompression of the small intestine by intubation.

It is needless to emphasize again the importance of immediate operative intervention in acute obstruction of the small intestine. In only a small percentage of cases is delay indicated for the purpose of improving the general condition of the patient.

The operation should be performed under spinal or ether anesthesia. An adequate and correctly placed incision is important. Frequently, from careful examination of the scout films of the abdomen, it is possible to localize the site of the obstruction and minimize the extent of abdominal exploration. When exploring the small intestine, it is preferable to explore the decompressed bowel below the site of obstruction in an upward direction, rather than handling the distended bowel above the site of obstruction. This, however, is not always technically possible.

If the distention is great, the bowel may be deflated by needle aspiration as suggested by Wangensteen.[5]

When resection is indicated because of gangrene, either an open or aseptic type of anastamosis can be done. The method used depends on the preference of the individual operator.

An end-to-end anastomosis is to be preferred to the side-to-side technique. However, in some cases, the proximal bowel may be so distended, as compared to the distal bowel, that a side-to-side anastomosis is preferable. Occasionally, in the desperately ill, poor-risk patient in whom a small bowel resection is indicated, an exteriorization procedure may be performed as a heroic measure. This, however, is to be avoided if possible.

During the operation for small bowel obstruction, it is essential to support the patient adequately by means of infusions and blood in order that a careful and unhurried operative procedure can be performed.

If the Miller-Abbott tube has previously been placed in the stomach with the tip at the pylorus, it may be possible, in a small percentage of cases, manually to pass the tip of the tube through the pylorus and facilitate subsequent decompression of the small intestine. Enterostomy is rarely indicated in the treatment of acute obstruction of the small intestine.

In all series of small intestinal obstructions, including the present cases, it has been shown repeatedly that the mortality varies directly with the length of time elapsing from the onset of the illness to the time of operative intervention, all other factors being equal.

Fluid replacement and correction of chemical disturbances are important in the treatment of all obstructions of the small intestine. As previously mentioned, the chemical disturbances which occur may be extremely severe and the patient will succumb if these are not adequately and quickly corrected.

Fluid replacement should begin as soon as the patient is seen, and continued through the operation and throughout the critical part of the postoperative period. The type of fluids to be administered depends on the location and duration of the obstruction and the chemical disturbances which have occurred. Each case should be carefully individualized. Chlorides, glucose, Hartmann's solution, sodium lactate, and other minerals are indicated.

The administration of whole blood is frequently necessary in acute obstruction of the small intestine. This is particularly true in cases in which gangrene has occurred.

In some cases of long-standing obstruction of the small intestine, marked hemoconcentration may be present. Whole blood, in addition to infusions, is indicated.

Decompression of the small intestine by means of some type of gastrointestinal intubation is the third important phase of the treatment of small bowel obstruction. The Miller-Abbott or some other type of small intestinal tube is the best means of decompressing the small intestine above the site of obstruction.

It must be emphasized, however, that the Miller-Abbott tube is not a substitute for operative intervention. It is merely an adjunct to operative treatment.

When the tube was first used, many mistakes were made by using intubation as a possible substitute for operation. Some patients died as a result of the delay in operation and the condition of many others was greatly jeopardized.

Frequently the Miller-Abbott tube is delayed in its entrance into the small intestine. However, if a large enough tube is used and the openings in the end are of sufficient size, the tube will act as a gastric or duodenal suction even though it does not pass farther down into the small intestine. Therefore, it serves the same purpose as a gastric or duodenal (Wangensteen) suction and nothing is lost.

Small intestinal intubation by means of the Miller-Abbott tube has definite advantages over enterostomy in that it is possible to decompress multiple loops of the small intestine, whereas the enterostomy will decompress only one isolated loop. Furthermore, the necessity of opening the small intestine for the per-

formance of an enterostomy permits possible intraperitoneal contamination and the probability of a subsequent small intestinal fistula, which may necessitate a further operative procedure for closure.

Enterostomy, however, still has some limited application in small intestinal obstruction due to adhesions, in which the patient is too markedly distended and is too ill to justify a more extensive procedure. Wangensteen[5] emphasized that this procedure still has merit.

In the treatment of small intestinal obstruction, there are several miscellaneous therapeutic measures which are also of importance. In markedly distended cases, the administration of a high concentration of oxygen will frequently assist in decompressing the small intestine. Morphine should be administered in regular doses because of its tonic and splinting effect upon the intestine. The application of heat to the abdomen is also thought to be of advantage in combating distention.

In the treatment of any acute mechanical obstruction of both the small and large intestine, the use of Prostigmine, Pituitrin, or other drugs to stimulate peristalsis, is definitely contraindicated. Enemas, flushes, or purgatives also should not be used. Until the ileus is definitely overcome, the patient should be given nothing by mouth.

Penicillin and streptomycin are indicated when resection of the intestine is necessary. Some surgeons recommend the use of sulfa drugs in addition to the antibiotics.

Colic Obstruction.—Immediate operation is indicated in all cases of acute colic obstruction except those cases of volvulus of the sigmoid in which it can be definitely determined that gangrene has not occurred. In such cases, proctosigmoidoscopic intubation of the colon will usually produce adequate decompression.

The operative treatment of acute colic obstruction due to carcinoma or diverticulitis differs from the treatment of acute obstruction of the small intestine in that these types of colic obstruction should be treated merely by decompression of the colon proximal to the obstructing lesion.

Conservative therapy, with or without gastrointestinal intubation and exclusive of proctosigmoidoscopic intubation in uncomplicated sigmoid volvulus, has little or no place in the treatment of any acute colic obstruction. In Fig. 13, in which the treatment of 103 cases of common colon obstructions has been analyzed, it is shown that of the nine patients treated conservatively, five died. This is a prohibitive mortality and well indicates the lack of success of conservative measures.

Immediate resection of an acutely obstructing colon lesion carries an extremely high mortality and is indicated only in colic volvulus with gangrene or in the occasional case of mesocolic thrombosis. In the present series, immediate resection was performed in eighteen cases with eight deaths, a mortality rate far higher than the over-all mortality of the entire series of colon obstructions.

The temptation to resect an acutely obstructing carcinoma of the colon is one to which many surgeons succumb. In this series, there were ten patients with acutely obstructing carcinomas treated by immediate resection, with a fatal outcome in five. In two of the survivals, the growth was shown to have been incompletely removed because of the haste necessary in performing the resection in the presence of the acute obstruction.

These results compare very unfavorably with those obtained in twenty-two patients with acutely obstructing carcinoma of the colon who survived a primary surgical decompression and later had resections. There was only one death, or 8 per cent, as compared to the 50 per cent mortality when resection was attempted in the presence of acute obstruction.

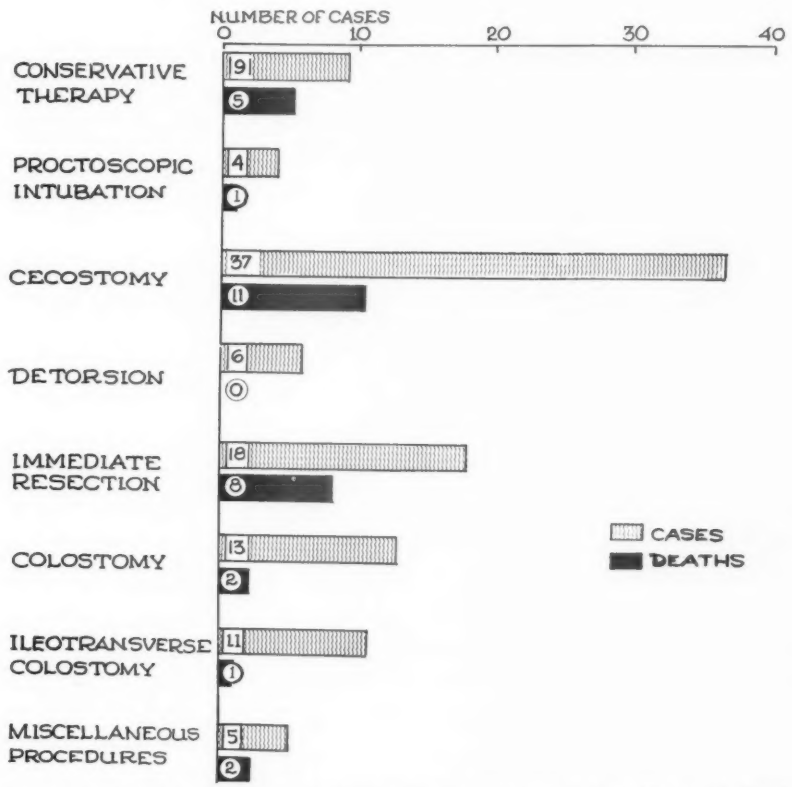

Fig. 13.—Distribution of therapeutic procedures in 103 cases (including 30 deaths) of acute obstructions of the large bowel. (From Marshall L. Michel, Jr., and Emit L. McCafferty, Arch. Surg. 1948.[6])

It must be remembered that the patient with acute malignant obstruction of the colon is in immediate danger from the obstruction, and is in remote danger from the primary disease, carcinoma. The surgeon's immediate concern at the original operation is to overcome the obstruction by proximal decompression, and any attempt to remove the carcinoma is definitely contraindicated.

The question whether or not to perform a cecostomy or a right transverse colostomy for acutely obstructing lesions of the left colon is one which is still being debated. In this series, thirty-seven cecostomies were performed with eleven deaths, and thirteen colostomies were performed with only two deaths.

Although the transverse loop colostomy is a somewhat more difficult procedure from a technical standpoint than the cecostomy, it is our opinion that the advantages of colostomy greatly outnumber the disadvantages. A colostomy can be performed aseptically and defunctionalization of the colon is more complete. Also, decompression is complete and can be obtained immediately if large catheters are passed down each of the loops of the colostomy. Early ambulation, which we believe is of importance, can be obtained more rapidly after a transverse loop colostomy than after a cecostomy. Wound infection and wound disruption are relatively common after cecostomy and uncommon after transverse loop colostomy. The main disadvantage of transverse loop colostomy is that it necessitates a second operative procedure for closing. However, because of the recent advances which have been made in colon surgery, such a procedure has become relatively simple.

For acute obstructing carcinomas of the right colon, the procedure of choice is ileotransverse colostomy, with or without cecostomy. Ileotransverse colostomy was performed on eleven patients in this series for acutely obstructing right-sided colon carcinomas, with only one death. If, at the time of operation, the cecum is found to be markedly distended, suggesting a competent ileocecal valve, a coincidental cecostomy can be performed.

There are two types of common colon obstructions in which the operative treatment differs fundamentally from that employed in obstructions due to carcinoma or diverticulitis. In volvulus of the sigmoid colon and intussusception, direct operative attack upon the obstructing lesion is indicated.

Volvulus of the colon occurs most often in the sigmoid region. In a recent series[11] of twenty-five cases of colic volvulus, sigmoid volvulus occurred in twenty-two.

In many cases of volvulus of the sigmoid, operative intervention, as an emergency measure, is not necessary due to the fact that proctosigmoidoscopic intubation of the sigmoid colon can frequently overcome the volvulus. In using this type of therapeutic procedure, one must be absolutely certain that there are no vascular changes in the wall of the bowel. In the present series, proctosigmoidoscopic intubation was performed in four patients with sigmoid volvulus, with one fatality. This death was the result of unrecognized gangrene of the colon.

Volvulus of the right colon and transverse colon should be treated by immediate operation. Detorsion should be performed, and some type of fixation can be attempted. Resection is indicated only if vascular changes are present. In cases of recurrent volvulus, resection should be performed as an elective interval procedure.

The technique of proctosigmoidoscopic intubation of the sigmoid colon in acute volvulus is worthy of mention. The procedure is best done with the patient in the head-down position. The proctoscope should be inserted under direct vision. Large amounts of air should not be injected into the colon. The condition of the mucosa must be carefully noted, and, if there is any suggestion of vascular changes, operative intervention is indicated. By carefully inserting

the sigmoidoscope, the distended loop of colon can be entered and it will usually suddenly and forcibly evacuate itself through the sigmoidoscope.

After adequate decompression has been obtained, a long soft rubber tube (28 to 30 caliber), approximately 15 inches long, should be inserted well up into the sigmoid colon. The tube should then be sutured to the anus and left in place for a period of two to three days.

Immediately following intubation, the abdomen should be checked carefully by means of a flat plate to be certain that the volvulus has been decompressed.

In cases of sigmoid volvulus in which there is a possibility of vascular changes in the wall of the intestine, or in which intubation has been unsuccessful, laparotomy with detorsion of the volvulus is indicated. After detorsion is performed, some type of fixation of the sigmoid colon to the lateral abdominal wall can be performed, and simultaneously a long rectal tube can be manipulated up into the sigmoid colon to maintain decompression for a period of several days.

In this series of cases, detorsion of an acute colic volvulus was done in six patients, with no deaths.

Colocolic intussusception is handled in essentially the same way as ileocolic intussusception. Direct operative attack is indicated for release of the obstruction. A detailed discussion of intussusception is not in the scope of this communication, as this form of intestinal obstruction in itself presents an individual problem with many ramifications.

In all cases of acute colic obstruction, gastrointestinal intubation of some type should be used. The Miller-Abbott tube can be inserted if the degree of small intestinal distention is marked. However, as mentioned previously, frequently the small intestinal distention is minimal and such energetic measures as the Miller-Abbott tube are not necessary. A gastric or duodenal suction will usually suffice.

In a recent series[6] of colic obstructions which we have studied, the use of the Miller-Abbott tube was greatly abused. Intestinal intubation was attempted, unfortunately, as a therapeutic measure to substitute for operation.

The Miller-Abbott tube was used in thirty-four patients, with fifteen deaths, a mortality much higher than the over-all mortality of all the colic obstructions. In ten of these, intubation of the small intestine was successful and there were six deaths, a 60 per cent mortality. This indicates that the surgeon had a false sense of security when intubation was successful, and operation was delayed, resulting in the high mortality.

On the other hand, in the twenty-four cases in which intubation was unsuccessful, there were only nine deaths. The surgeon fortunately was forced to operate because he was unsuccessful in intubating the small intestine and the patient thereby was better off.

In a further breakdown of these thirty-four cases, in the thirty-two patients who were operated upon, there were thirteen deaths. On the other hand, two of the patients were not operated upon and both died.

This indicates the harm that can be done by the injudicious use of the Miller-Abbott tube as a substitute for operation in the treatment of colic obstruction. Similar errors have been made in the handling of acute small intestinal obstruction.

The patient with an acute colic obstruction should be adequately supported by means of fluid and blood. However, the problem of chemical imbalance is rarely severe in colon obstruction, and fluid replacement is a relatively simple problem.

It must be remembered that these patients frequently fall into the old age group, and will not tolerate large amounts of rapidly administered fluids, particularly saline solution. The miscellaneous therapeutic measures listed under the treatment of small bowel obstruction (such as morphine, oxygen, vitamins, heat) also have a place in the treatment of colon obstructions.

SUMMARY AND CONCLUSIONS

1. Recent reports reveal a continued high mortality in acute intestinal obstruction.

2. An analysis of 258 cases of acute intestinal obstruction is presented.

3. The differences between acute obstruction of the small intestine and acute colic obstruction are manifold.

4. These two types of obstruction differ in the following categories: etiology, incidence, age, physiology, pathology, laboratory findings, x-ray findings, clinical picture, surgical risk, treatment, and mortality.

5. For a clear understanding of mechanical ileus it is essential that colic obstructions in general be set apart from obstructions of the small intestine.

6. The subject of intestinal obstruction is by no means a closed issue. The continued high mortality rate indicates the necessity of further clinical and experimental studies.

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Case Reports

OBSTRUCTIVE JAUNDICE AS A COMPLICATION OF DUODENAL ULCER

A Case Report

ROGER D. WILLIAMS, M.D., COLUMBUS, OHIO

(From the Department of Pathology, Ohio State University)

PARKS and Fitz,[1] in 1939, reviewing thirty-six cases of duodenal ulcer with obstructive jaundice, called attention to the rarity of this complication in the experience of gastroenterologists from leading clinics in this country and in Europe. In 1942, Levine and Gordon[2] reported a case of obstructive jaundice following perforation of a duodenal ulcer, which was relieved following the closure of the duodenal perforation. A survey of 2,650 cases of duodenal ulcer reported in the literature revealed clinical jaundice in only one case. Engel and Spann,[3] in 1946, reported a case in which the jaundice was believed to have been caused by perforation of a duodenal ulcer; they explained jaundice in their case and in that of Levine and Gordon as a result of obstruction caused by acute inflammatory edema in the gastrohepatic ligament.

Because of the obvious rarity of this condition and its interesting and as yet not fully understood mechanism, we wish to present the following case of chronic duodenal ulcer with obstructive jaundice.

CASE REPORT

J. B. (St. Francis Hospital No. 49266), a 55-year-old white man, was admitted to the medical service with complaints of bleeding from the rectum for twelve hours and continuous jaundice for five months. On Aug. 26, 1948, he had been admitted to another hospital with jaundice of two weeks' duration, the jaundice having been first noted by his friends. At that time he had had no abdominal pain, nausea, vomiting, or history of serum injections. He had, however, noted an increased bulk of the stools, which were light colored and foul smelling. The physical examination was negative except for moderate epigastric tenderness and enlargement of the liver 3 cm. below the right costal margin. There was a hemoglobin of 13.4 Gm., a red blood cell count of 4.45 million, and a normal white cell count and differential. The urine was essentially negative. The van den Bergh reaction was direct positive with a blood bilirubin of 10 mg. per cent. The urobilinogen content of the feces was only 6 mg. per 100 Gm. of feces. The cephalin flocculation test was negative. A chest x-ray film showed no abnormalities. A gastrointestinal x-ray series was not carried out. Following surgical consultation the patient was discharged with the diagnosis of inoperable carcinoma of the pancreas with common duct obstruction.

On entrance to St. Francis Hospital, the patient stated that he had had continuous jaundice and intermittent pruritus for five months and had slowly lost twenty-five pounds in weight. He still had no abdominal pain, nausea, or vomiting. Five days before admission he had noted for the first time tarry stools. He came to the hospital because of the passage of bright red blood from the rectum twelve hours before admission.

The physical examination revealed a well-nourished but pale and moderately jaundiced white man. The liver extended 5 cm. below the right costal margin, and one

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observer felt a firm, poorly defined mass below its mid-portion. Rectal examination showed black feces and bright red blood on the examining glove.

On admission, the hemoglobin was 4.0 Gm., the red cell count 1.25 million, and the white cell count 11,200. The blood serology was negative. The thymol turbidity reaction and the cephalin flocculation tests were within normal limits; the blood total proteins were 3.85 Gm. per cent with a complete reversal of the albumin-globulin ratio. The van den Bergh reaction was direct positive with blood bilirubin of 10 mg. per cent. The urine gave a positive test for bile but a negative reaction for urobilinogen.

The patient was given approximately 1,000 c.c. of whole blood by transfusion daily during his hospital stay. However, the hemoglobin did not rise over 6.0 Gm., and he continued to show evidence of bleeding from the intestinal tract with both tarry and bloody stools. He was considered to have carcinoma of the pancreas with common bile duct obstruction, metastases to the liver, and involvement of the duodenum with hemorrhage. His condition became progressively worse, and he expired on the eighth day after admission.

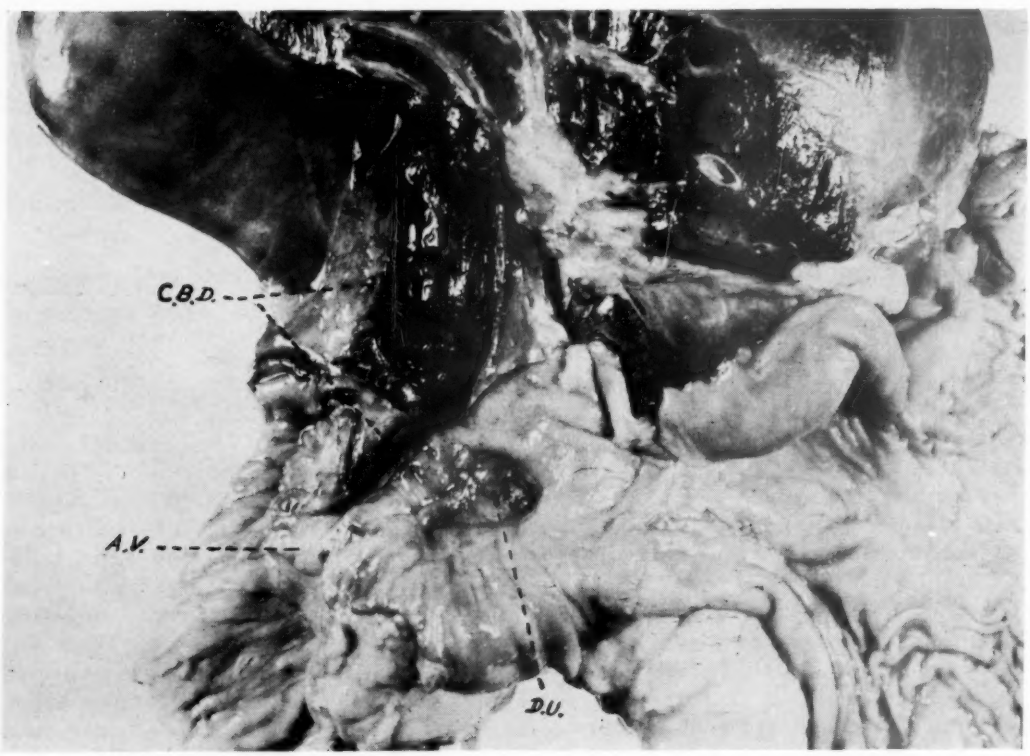

Fig. 1.—Gross specimen showing relationships of common bile duct (*C.B.D.*) and ampulla of Vater (*A.V.*) to the duodenal ulcer (*D.U.*).

At autopsy the patient was found to have been a well-developed and well-nourished, jaundiced, middle-aged white man measuring 168 cm. and weighing 140 pounds. The peritoneal cavity contained approximately 2,000 c.c. of clear, bright yellow fluid. The heart showed only slight atheromatous thickening of the coronary arteries, and the lungs were normal. The spleen was enlarged and soft and weighed 300 Gm. The liver weighed 1,900 Gm. It cut with increased resistance and showed a fine nodularity. The larger intrahepatic bile ducts were prominently dilated, and the parenchyma was jaundiced. The gall bladder was dilated, thick walled and contained approximately 200 c.c. of thick green mucoid bile. The common and hepatic ducts in the gastrohepatic ligament measured 1.5

cm. in diameter. The common duct was narrowed to a diameter of 1 to 2 mm. at the place where it passes through the head of the pancreas in close proximity to the posterior wall of the duodenum. It was embedded in dense scar tissue involving the duodenal wall and the head of the pancreas. The pancreas contained a large multiloculated cyst, measuring 8 by 3 by 2.5 cm., which communicated with the duodenum through a stenosed pancreatic duct lying in dense scar tissue at the head of the pancreas and at the base of the duodenal ulcer. The tail of the pancreas showed small irregular lobules of parenchyma separated by an increased amount of dense white connective tissue. The entire intestinal tract was distended and filled with dark red blood. Four and one-half centimeters distal to the pylorus on the posterior wall of the duodenum there was a large ulcer, measuring 2.5 by 2 cm. in diameters and 4 to 6 mm. in depth. In its central portion there was a small eroded blood vessel. The ulcer had penetrated to the head of the pancreas and its base was formed by dense scar tissue in the pancreas. Through this scar tissue passed the duct of Wirsung, which could be probed only with difficulty. The duodenal portion of the common bile duct coursed along the inferior margin of the base of the ulcer and was surrounded by the same scar tissue which involved the pancreas. The ampulla of Vater was approximately 6 mm. distal to the mucosal margins of the ulcer. The other organs examined at autopsy showed no gross pathologic changes.

Histologic examination included tissue taken from the duodenum, the ulcer, common bile duct, and a portion of the head of the pancreas just beneath the ulcer. The base of the ulcer was composed of dense hyalin scar tissue showing only slight lymphocytic infiltration and little fibroblast proliferation. There was a segment of intact mucosa between the ulcer and the common bile duct, which showed lymphocytic infiltration. The common bile duct was surrounded by dense, hyalinized scar tissue which extended from the base of the ulcer into the head of the pancreas. The head of the pancreas showed extensive fibrosis with more than one-half of the parenchyma replaced by scar tissue. There was pressure atrophy of groups of acini and irregular dilatation of smaller pancreatic ducts. In addition, there were larger cysts irregularly lined by flattened cuboidal epithelium. Sections from the tail of the pancreas also showed a rather prominent fibrosis. The liver showed biliary cirrhosis with proliferation and dilatation of bile ducts which were partially filled with bile thrombi. Sections of other organs showed no noteworthy changes.

COMMENT

This case is interesting from the standpoint of the pathologic anatomy which it presents and its diagnostic and therapeutic problems. Two etiological factors must be considered in the production of obstructive jaundice in this case: the fibrosis of the head of the pancreas which was traversed by the common bile duct and the duct of Wirsung, and the extensive scarring at the base of the ulcer.

It is fairly well established that chronic pancreatitis can cause obstructive jaundice.[4] In 1932, Walters and Dehne[5] reported 113 cases of obstructive jaundice due to chronic pancreatitis. In 1938, Fraser[6] collected from 172 physicians in the British Isles 1,035 cases of obstructive jaundice in pancreatic disease. Of these, 238 (or 23 per cent) were considered due to chronic pancreatitis. Walters[7] reported that 15 per cent of the patients operated upon at the Mayo Clinic up to 1938 for relief of common duct obstruction due to tumors were alive and well five years after surgery, and that the diagnosis of pancreatic malignancy had to be changed in these cases to that of chronic pancreatitis. Since in our case the duct of Wirsung was stenosed at the base of the ulcer, its obstruction might well have been the major cause of a diffuse pancreatitis followed by the extensive fibrosis which was seen in the pancreas.

Although some cases of acute and chronic pancreatitis may occur as a result of penetrating ulcer of the posterior wall of the duodenum, Bockus[8] stated that the pancreas usually resists the effects of adherent penetration without the occurrence of a generalized pancreatitis. We therefore expect such inflammation as occurs with penetrating peptic ulcers to remain localized in adjacent parts of the pancreas.

The pancreatic and duodenal portions of the common bile duct lie in the second portion of the duodenum, and the ampulla of Vater usually empties into the duodenum 7 to 10 cm. distal to the pylorus. The majority of chronic ulcers of the posterior wall of the duodenum, however, occurs in the first 5 cm. beyond the pylorus. Portis and Jaffe[9] reported that only 15 per cent of 158 duodenal ulcers from 9,171 consecutive autopsies were more than 5 cm. from the pylorus, and these ulcers were relatively small. The larger ulcers lie proximal to that portion of the duodenum behind which course the common bile duct and the large pancreatic ducts. In the case presented, an ideal but rare situation for obstruction of both common bile and pancreatic ducts occurred. The ulcer was large, occurred 4.5 cm. distal to the pylorus, and was located in the posterior wall of the duodenum. The common bile duct coursed along the inferior margin of the ulcer crater with the ampulla of Vater less than 1 cm. from the mucosal margin of the ulcer.

From the standpoint of diagnosis it should be stated that the erroneous diagnosis of obstructive jaundice due to carcinoma of the head of the pancreas made in this case is not unusual. However, it illustrates the need for early and adequate studies in similar cases. With so few cases in the literature, little can be gained from their study which could be directly helpful in diagnosis. In the thirty-six cases reported by Parks and Fitz, the age incidence was 20 to 54 years; there was a predominance of men to women of four to one; upper abdominal pain prior to the onset of jaundice was frequent; and a few cases presented only painless jaundice. To these should be added the relatively mild weight loss after prolonged jaundice, which is characteristic of benign lesions as compared with the more marked weight loss occurring with malignant tumors of the pancreas and gall bladder.

Treatment in similar cases should not await accurate diagnosis. If an ulcer can be demonstrated, treatment of the ulcer may relieve the biliary obstruction; however, radiologic evidence of an ulcer is occasionally absent. Whether the causation of obstruction is known or not, surgery for the relief of the obstruction is imperative. The relief of pruritus and the other discomforts of obstructive jaundice, even in malignant disease, justifies surgery.

SUMMARY

A case of chronic obstructive jaundice complicating a large bleeding duodenal ulcer is presented. At autopsy the biliary obstruction was found to be due to fibrous scar tissue involving the head of the pancreas and the base of the ulcer. This case also presented an obstruction of the pancreatic duct with fibrosis and cyst formation in the entire pancreas.

Since benign lesions in the duodenum and pancreas may clinically simulate malignancy, all patients with progressive obstructive jaundice should be operated upon for the relief of the obstruction.

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ACUTE JEJUNOGASTRIC INTUSSUSCEPTION

Report of a Case

T. Richard Watson, Jr., M.D.,* and Walter B. Crandell, M.D.,†
White River Junction, Vt.

(From the Veterans Administration Hospital, White River Junction, Vt.)

JEJUNOGASTRIC intussusception, although rare, is a definite entity and presents certain striking diagnostic features. It usually is a late complication of a gastroenterostomy or gastrectomy in which either or both of the jejunal limbs intussuscept through the stoma into the stomach.

Aleman[2] attributes the description of the first recorded case to Bozzi in 1914 and the second to Steben in 1917. Warren[8] followed with a third case report in 1919. To date, seventy-three cases have been recorded, seventeen in the American literature. Since the excellent and comprehensive review by Aleman in 1948 in which he also added two cases, we have found one further case.[5]

The preoperative clinical diagnosis has been made only rarely, but fourteen cases have been diagnosed before operation with the aid of x-ray examinations. The mortality rate is stated to be 10 per cent for cases in which operation is performed within the first forty-eight hours after the onset of symptoms and about 50 per cent when the operation is delayed. The importance of an early diagnosis is therefore apparent.

The case here presented is unique and "complete" since the preoperative clinical diagnosis was made and confirmed by a pathognomonic x-ray picture, the intussusception was found at operation, reduced, and recovery was uneventful.

CASE REPORT

L. S., a 60-year-old white unemployed man, was admitted to the Veterans Administration Hospital, White River Junction, Vt., for the fourth time on Nov. 22, 1948, complaining of eructation following meals, and intermittent, dull, aching, right upper quadrant pain. On previous admissions he had been treated for chronic bronchitis, pulmonary emphysema, and osteoarthritis of the lumbar spine and hip joints. The diagnosis of chronic cholecystitis and cholelithiasis was established by Graham test during his preceding admission in June, 1948. He had been discharged on a conservative regime to return for cholecystectomy if not relieved of his distress.

On Nov. 29, 1948, a cholecystectomy and exploration of the common duct were done. The patient's postoperative course was uneventful until the seventh day. At that time studies were performed to determine the effect upon the electrocardiogram of alterations of pressure within the common duct. Subsequently the patient developed a peritonitis localizing in the right upper quadrant and in the pelvis. This gradually resolved an antibiotic therapy, but he continued to complain of anorexia, occasional nausea and vomiting, and right

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*Acting Assistant Chief of Surgery and Former Resident in Surgery, Veterans Administration Hospital.

†Chief of Surgery, Veterans Administration Hospital; Assistant Professor of Clinical Surgery, Dartmouth Medical School.

upper quadrant and right lower quadrant abdominal pain. There was marked constipation. Following removal of the common duct T tube February 12, the sinus continued to discharge yellow fluid intermittently and the patient had episodes lasting three to four days with temperature elevations to 101° F. Radiologic examination of the upper gastrointestinal tract showed persistent irregularity of the duodenum. Proctoscopy and a barium enema showed a constriction of the rectosigmoid 15 cm. from the external sphincter.

On April 25, 1949, a lysis of pelvic adhesions was done. These were firmly constricting the sigmoid and thought to be residuals of a pelvic abscess. No evidence of neoplasm was noted. Because of signs of partial duodenal obstruction, and the duodenal abnormality seen by x-ray examination, exploration of the region of the duodenum and common duct was considered advisable. There were dense adhesions and the structures could not be completely defined. During this procedure the duodenum was inadvertently opened. Closure by suture was difficult because the tissues were extremely friable. A posterior gastroenterostomy was done to relieve the patient's symptoms of partial duodenal obstruction and aid healing of the perforation. The gastroenterostomy stoma was 3 cm. in diameter at the conclusion of the procedure.

Fig. 1 *A*.

Fig. 1, *A*, *B*, and *C*.—Acute jejunogastric intussusception. Preoperative radiograms of stomach showing the mucosal folds of intussuscepted jejunum within the stomach.

For thirty-six days postoperatively the patient's course was satisfactory except for the necessity of evacuating a wound hematoma on the tenth day. On May 24, 1949, radiologic examination showed a persistently deformed duodenal cap but the gastroenterostomy functioned well and the stomach was of normal size.

On June 1, 1949, the patient noted the onset of moderate, constant, mid-epigastric pain which did not radiate, and he vomited once on June 2 following a meal. On June 3 he complained of a feeling of fullness in the stomach and vomited food after each meal with

the mid-epigastric pain becoming progressively worse during a period of eight hours. At 7 P.M. he vomited bile, and one hour later approximately 1,000 c.c. of bright red fluid. Examination at this time showed the patient to be uncomfortable, but he did not appear acutely ill. Temperature was 98° F. and pulse 78. The abdomen was soft with moderate central epigastric tenderness, and a soft, movable mass could be palpated in the left upper quadrant under the costal border. The abdominal pain had been decreasing for one hour. The diagnosis of jejunogastric intussusception was considered at this time but bleeding ulcer was thought to be most likely. The next morning the patient was still uncomfortable and vomiting copious amounts of a thin, watery, wine-colored fluid in spite of constant gastric drainage by an inlying, transnasal tube attached to Wangensteen suction. He complained of a persistent, fairly severe pain, and a firm, freely movable, moderately tender mass 8 to 10 cm. in diameter could readily be felt just below the xiphoid in the angle of the costal arches. The left costal arch prevented delineation of its cephalic and lateral borders.

Fig. 1 *B*. (For legend see preceding page.)

That morning a diagnosis of jejunogastric intussusception was made. Radiologic study was advised to confirm the diagnosis before operative reduction. The examination was made with a small amount of barium and revealed the stomach to be huge, with numerous markings of jejunal mucosa in the stomach, pathognomonic of jejunogastric intussusception (Fig. 1).

Exploration was promptly carried out. By actual measurement, 50 cm. of the efferent jejunal limb were found to have passed through the gastroenterostomy stoma into the stomach. This intussusception was easily reduced with bimanual manipulation. The distal 10 cm. of the afferent limb and the proximal 60 cm. of the efferent limb were edematous with numerous hemorrhagic areas in the subserosa. However, there was no evidence of

gangrene. Following reduction the stoma was 10 cm. in diameter. The efferent jejunal limb was then fixed to the anterior parietal peritoneum with widely spaced interrupted silk sutures.

Postoperatively the patient's course was uneventful. On June 16, 1949, a gastrointestinal series again showed the stomach to be of normal size with a well-functioning gastroenterostomy stoma. The persistent irregularity of the duodenal cap remained. The patient was discharged asymptomatic on July 18, 1949.

DISCUSSION

The seventy-three recorded cases of jejunogastric intussusception have been classified by various authors according to their clinical, anatomic, and radiologic characteristics.[1, 2, 6] By definition all cases must have a history of gastric surgery. The clinical divisions based upon the history and physical findings are those of acute and chronic, as emphasized by Adams.[1] The case presented is an example of the acute type characterized by the sudden onset of epigastric pain accompanied by persistent vomiting, first of food, then of bile, and finally of blood.

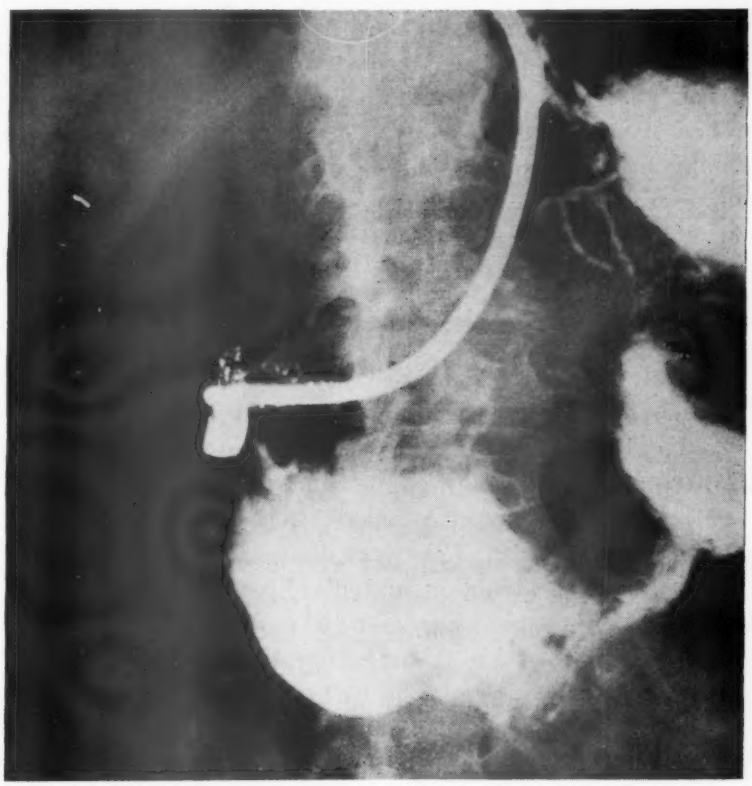

Fig. 1 *C*. (For legend see page 117.)

In establishing a preoperative diagnosis of jejunogastric intussusception as opposed to a bleeding duodenal ulcer there were several important considerations. The first of these was the history of previous gastric surgery. Second, the hematemesis was different from that produced by a bleeding peptic ulcer. At first it was bright red, copious, thin, and fluid. Later it was purple red

suggesting extravasation of venous blood which was vomited before it had been acted upon by gastric secretions. In addition to this, the mid-epigastric pain remained constant, though varying somewhat in intensity. It was notable that the patient did not appear particularly ill and the temperature and pulse remained normal. The final diagnostic feature was the movable, large, soft, palpable mass in the epigastrium.

Roentgenologic examination confirmed the clinical diagnosis. This confirmation by x-ray view has been recorded in fourteen other cases in the literature and we advocate this procedure, employing a thin barium mixture. We have found but two examples of this type of radiogram published in the American literature (Chamberlain[3] and Wangensteen[7]), although Aleman[2] has collected and published several, including two cases reported by him.

The three anatomic types of jejunogastric intussusception first described by Shackman[6] have been reviewed by various authors.[2, 4] In type I, the afferent loop alone intussuscepts into the stomach; in type II, there is intussusception of the efferent loop, and in type III, both afferent and efferent loops intussuscept into the stomach through the stoma. According to Aleman, there are four cases where the intussusception has occurred following subtotal gastric resection rather than gastroenterostomy. There are also three cases in which the efferent loop has intussuscepted through an enteroenterostomy into the stomach.

A roentgenologic classification is used by Aleman and consists of *simple* intussusception, corresponding to anatomical types I and II, and *combined* intussusception, corresponding to anatomic type III. The present case was an example of a simple intussusception, of the anatomic type II.

SUMMARY

A case of acute jejunogastric intussusception is presented which is unique in that it might be considered "complete," since the diagnosis was made clinically, confirmed by radiologic examination, and at operation a successful reduction was performed and followed by uneventful convalescence.

The most important diagnostic features are briefly discussed. They are: (1) previous gastric surgery, (2) persistent emesis including hematemesis suggesting both pyloric obstruction and bleeding ulcer, (3) constant mid-epigastric pain, (4) an epigastric mass, and (5) an outline of small bowel mucosa within the stomach revealed by a barium swallow.

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Editorial

Blood Transfusion and Civil Defense

WHETHER in peace or in war, the objectives of the practice of medicine are essentially similar. Measures which promote the welfare of the patient in civilian practice are likely, therefore, to prove beneficial in the treatment of casualties resulting from natural catastrophes or from enemy action. Certainly the improvement of facilities for blood transfusion serves this twofold purpose. Blood banks established in Great Britain during World War II were of such inestimable value in the treatment of bomb injuries that they have been continued since the war as part of the standard armamentarium in the care of patients whose diseases result from natural or accidental causes.

The first blood bank was conceived and operated by O. H. Robertson, an American working with the British army in 1916, but the idea received little attention until 1937, when a blood bank was established in Cook County Hospital. Since then there has been a slow but steady increase in the number of hospital blood banks serving the patients of single institutions. With the entrance of America into World War II another approach to the problem of supplying blood was developed in this country. At the request of the Armed Forces the American Red Cross created a blood donor service with centers in large cities where blood was collected, initially for processing into plasma, later to be shipped to the theaters of operation as whole blood. Since the war the Red Cross has developed a national blood program in which blood is collected in regional centers, or carried to them, and is supplied to the hospitals of the region for transfusion to patients. This program is being expanded as rapidly as circumstances permit.

So far, however, neither the officials of the federal government nor the members of the medical profession have been forced to plan realistically to sustain attacks by a hostile power. From data accumulated at Nagasaki and Hiroshima it has been estimated that 5,000,000 pints of blood would be required in three weeks to treat the casualties resulting from ten atomic bombs dropped simultaneously on as many cities in this country. This is approximately one-half the amount collected by the Red Cross in this country during the entire war. Probably none of the cities thus attacked could supply blood for the wounded because all services would be disrupted. Blood would necessarily be shipped from other regions to the places to which the injured had been evacuated.

This problem indicates the absolute necessity for some type of a national blood transfusion service, and there is general agreement that it should be operated by the American Red Cross. Since an enemy attack is to be expected without warning, there is a corollary that the transfusion service should function actively in time of peace with the ability to expand greatly at a moment's notice.

A national blood transfusion service not only must be an integral component of peacetime medicine, but plans must be made and executed in advance for the collection of blood in diverse regions of the country and the shipment

of large amounts for use in far distant places. Since transfusion equipment cannot be manufactured in large quantities overnight, the situation demands the stock-piling of five to ten million sterile sets of equipment for the collection, shipping, and administration of whole blood. What governmental or public agency is now empowered or financed to accomplish such stock-piling? Furthermore, there are many types of transfusion equipment made commercially in this country today. Most have been carefully designed so that parts produced by one manufacturer are not interchangeable with those of another. In a nationwide emergency some standardization of equipment is urgently desirable. By what means is such standardization to be accomplished? Is it to be by voluntary agreement or by governmental decree?

The national blood program of the American Red Cross is in operation in a number of regional centers, whence the blood is transported to the hospitals of the region for transfusion. In many cases this has proved convenient for the hospitals so served, and some hospital blood banks have been discontinued. There is no doubt that the centralization of blood collection has certain advantages, especially in its administrative aspects. But, on the other hand, the individual hospital seems the logical unit for a transfusion service. In the hospital major surgical operations are performed which require most of the blood transfusions in modern medical practice. To these hospitals come the friends and relatives of the patient, and these persons are psychologically the most willing blood donors. Also, the members of the hospital staff are those best acquainted with the condition of the patient and are the logical ones to ask for blood donations. Furthermore, even with a centralized arrangement for the collection of blood, each hospital receiving blood must maintain facilities and personnel for the storage of blood and the performance of blood grouping and cross-matching.

In time of national disaster the physician or surgeon will surely have to face another problem for his own patients. Suppose that his hospital is dependent on a regional center for supplies of blood. When a national emergency suddenly occurs, the tendency will be to send all available blood to the point which has sustained attack. The regional centers may not be able to supply blood for normal civilian needs because of this demand, or the center itself may be destroyed.

At the present time a committee of the American Medical Association is compiling the results of a recent survey of hospital blood banks in the United States. Preliminary estimates show that there are only about 1,500 blood banks in this country, although the number of hospitals of various sizes is over 6,000. Experience has shown that a blood bank can be operated successfully in a hospital with a capacity of 200 beds or over. Attempts should be hastened to establish banks in every hospital of sufficient size to improve the medical care in time of peace and to serve as insurance in time of war. It is to be hoped that some suitable arrangement will be made to integrate the hospital blood banks of the country into a national blood transfusion service which will exploit the advantages of decentralization.

—Elmer L. DeGowin, M.D.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE GENESIS OF GASTRODUODENAL ULCER FOLLOWING BURNS

AN EXPERIMENTAL STUDY

STANLEY R. FRIESEN, M.D.,* MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota Hospitals)

INTRODUCTION

FOR over one hundred years the interesting, but unusual, occurrence of gastroduodenal ulceration following superficial burns in human beings has aroused keen comment and study among clinicians and investigators alike. Numerous and pleomorphic theories have been offered to account for ulceration after a severe burn, but there is no agreement among the theories as to its genesis.

The purpose of this study was to determine, if possible, the etiological agent responsible for the development of gastroduodenal ulceration following extensive burns.

HISTORICAL REVIEW OF THE PROBLEM

Although Curling's[24] comprehensive report, in 1842, concerning the occurrence of intestinal ulceration following burns directed especial attention to the subject, proper commemoration should also be made to Swan[115] who, in 1823, reported a case with ulcers of the stomach following burns. In this same year Cumin,[23] in dissections upon individuals with fatal cases of severe burns, reported inflammation of the gastrointestinal tract, but failed to note ulceration. In 1832, Dupuytren[30] called attention to the violent congestion, severe gastroenteritis, and ulceration of the stomach and duodenum following burns in a reported case. As acknowledged by Curling[24] in his report, Cooper[22] and Long[81] also deserve a measure of priority; Cooper, in 1839, reported three cases of duodenal ulcer following burns (two of which were later quoted by Curling), and Long, in 1840, described two instances of fatal burns in which perforation of duodenal ulcers occurred. Long also quoted Liston[79] as recording one case. Curling's report included four cases of his own observation, two furnished by friends (Mr. Stanley of St. Bartholomew's Hospital, London, and Mr. Henry Lee of St. George's Hospital, London), and the four previously recorded by Cooper and Long, making a total of ten cases, which, he stated, "Considering the rarity of ulceration in this part of the tube, and the absence of any previous symptoms of intestinal affection, appear to me sufficient to indicate the existence of a connection between the injury to the skin and the disease in the duodenum." All ulcers in the ten cases reported by Curling were situated in the duodenum.

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This paper is an abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Surgery, June, 1949 (Dr. Owen H. Wangensteen, Thesis Advisor).

*Now with the Department of Surgery, University of Kansas Medical Center, Kansas City, Kan.

Many case reports followed the collected series of Curling in 1842, and still being reported sporadically. Collected series of cases, aside from individual case reports, are not frequent, however. The most complete series is that of Harkins,[53] in 1938. Harkins' extensive review includes a report of a case, with a study of 107 cases collected from the literature, 94 with necropsy, 13 with recovery, and some experimental studies.

The frequency with which gastroduodenal ulceration follows superficial burns is difficult to determine because of the following circumstances: (1) a majority of collected series are based on the compiled records of a number of authors; (2) many patients succumb to the burn a few hours after receipt of the injury, a period of time too short for the development of ulceration, and necropsy is not done in many of these instances; (3) some patients, having developed ulceration following burns, may go on to recovery without clinical demonstration of the complication; and (4) local and systemic therapy on the burned patient may alter the incidence of gastrointestinal ulceration, and certainly will affect the number of patients dying of the burn and subjected to necropsy. However, many reports are available as to the incidence of Curling's ulcer in cases in which necropsy has been done. This incidence varies, according to investigators, from 0.0 per cent to 36.4 per cent. Harkins[53] noted one case of duodenal ulcer in four fatal burns, and in his extensive review of the literature determined the average incidence to be 3.8 per cent (26 ulcers among 680 necropsis of individuals with fatal burns). This average figure (3.8 per cent) is identical with that revealed in a review of the autopsy records of the Department of Pathology, University of Minnesota, by Mears,[87] in 1947. He found that from 1926 to 1944, there were 156 necropsies performed on individuals dying of burns, and of these, six (3.8 per cent) exhibited acute gastrointestinal findings. The average incidence of 3.8 per cent as determined by Harkins is in close agreement with that reported by Simmonds[109] in 1898, and by Perry and Shaw[97] in 1893, who stated that 3.3 per cent of those dying of burns exhibited duodenal ulceration, while only 0.4 per cent of persons dying of all causes showed acute ulceration of the duodenum, admitting "an undoubted relationship between the cutaneous and intestinal lesion."

The pathologic changes which occur most commonly in the gastrointestinal tract following burns consist of hyperemia and congestion,[94, 55] a condition to which I have called attention experimentally.[39] It is interesting to note that a significant relationship of intestinal congestion to fatal superficial burns was drawn by Dupuytren[30] in 1832, in one of the first recorded articles concerning the pathologic effects of burns. Gastrointestinal congestion, as well as generalized visceral congestion, is noted in practically all necropsy reports of individuals with fatal burns, even within a few hours after receipt of injury. An extensive review of pathologic changes in patients with burns was given by Pack[94] in 1926. He stated that duodenal ulcers following burns are generally single, but may be multiple and may be located at various levels from the upper transverse duodenum to the descending portion, close to the bile duct. The ulcers may vary in size from a pinhead to a quarter. The result is perforation, hemor-

rhage, or spontaneous healing. Four cases of esophageal ulcer, two with perforation, following burns have been reported (Robinson,[103] 1943, Rankin,[101] 1945, Humphrey,[67] and Fisher[36]).

Theories as to the Genesis of Curling's Ulcer.—Representative of the intense interest, clinically and experimentally, in the subject of Curling's ulcer, is the voluminous number of theoretical accounts of the etiology and genesis of this condition, a number almost equal to the number of observers. Many of the recorded theories have been discarded with the development of newer concepts of physiology, and so forth, but a few are prevalent at the present time with no unanimity of choice. These form the basis of the present work. For the purpose of a more fluent and logical presentation from the literature of these many theories, propounded by many observers, certain groups have been collected under more general classifications. At least thirty individual theories have been recorded.

Compensatory Hypertrophy of Brunner's Glands.—Curling,[24] in 1842, believed that these glands sympathized and compensated for the suppression of skin exhalation by an increased activity. This, in turn, led to an irritation which caused inflammation and ulceration.

That the skin itself may play no role in the development of visceral changes in burns is suggested by the oft-quoted case of Leonard and Dayton,[76] who reported that the prolonged treatment of an inoperable carcinoma of the cervix by low heat (Percy's "cold iron" method) resulted rapidly in a fatal outcome with lesions, including duodenal ulcer, similar to those in cases of fatal cutaneous burns. Close scrutiny of this report reveals a marked element of sepsis, and there are no data concerning the relative concentration of blood in this patient. Many authors disregard this case as an example of ulcer following burns.

Spinal Reflex From Burned Skin, and Other Theories Relating to Reflex and Neurogenic Origin.—In 1858, Brown-Séquard[13] reported that, in experimental animals, visceral congestion did not occur within three days after carbonization of a lower limb when the reflex arc was interrupted by high section of the trunks of the sciatic and crural nerves. This work refers to congestion rather than ulcers, and the results are obtained, chiefly, from only two cases. Cooke[21] believed the antiferments of the mucous cells are reflexly destroyed, and Pack[94] listed a theory in which he stated that a reflex inhibition of intestinal circulation causes the ulcer. Kabat and Hedin,[71] 1942, noted, among other things, that cats in which spinal transection, to interrupt the reflex from the burned area, had been carried out developed a less marked hemoconcentration and local fluid loss than control animals, but that there was no difference in the visceral pathology of the two groups of animals.

Nervous influences were thought to be of importance in the etiology of Curling's ulcer by Paget[96] in 1890, in a report of a case, because of the proximity of the great sympathetic plexuses. Wilson,[138] in 1935, thinking the ulcer secondary to a hypothalamic lesion, searched for such a lesion in one of his cases with negative results. This hypothesis was not without merit in view of Cushing's[25] description, in 1932, of cases of peptic ulcers in patients with hypothalamic lesions.

Theory of Direct Action of Heat on Intestines.—Underhill, Kapsinow, and Fisk,[120] in 1930, measured the intra-abdominal temperature in rabbits experimentally burned on the abdomen. They stated that if the heat penetrated the abdominal cavity, most of the macroscopic changes characteristic of burns were present in their experimental animals, but on the other hand, if the burn was remote from this region nothing abnormal was noted except for some congestion. It is significant, however, that congestion was noted in the latter group of animals, for it is a common occurrence associated with burns of any region of the body, and a circumstance probably precursory to Curling's ulcer.

The Theory of Hemoconcentration and Other Related Theories, Including Stasis, Low Blood Volume, and Physical Theory.—The first of these theories is a relatively recent one in the genesis of Curling's ulcer, although the occurrence of hemoconcentration in burns had been noted as early as 1862.[3] General visceral changes were attributed to it by Pack,[94] but there is only one report, other than mine,[39] in which hemoconcentration, per se, is suggested as the cause of Curling's ulcer—that by Kapsinow[72] in 1934. He presented no statistical proof or experimental confirmation of his suggestion. The proportionate incidence of gastrointestinal congestion with the occurrence of hemoconcentration in burns of experimental dogs has recently been reported.[39] Among numerous reports of hemoconcentration in burns, Locke[80] noted, in severe but not fatal cases, increases in the number of erythrocytes from 1,000,000 to 2,000,000 per cubic millimeter of blood. In fatal cases, the increase is often from 2,000,000 to 4,000,000 per cubic millimeter of blood. The hemoglobin has been found to be concomitantly elevated; Underhill and co-workers[119] studied twenty-one burned patients with a hemoglobin of 117 to 209 per cent. Experimentally, hemoconcentration in burned animals has also been noted by Blalock[8] and his associates and Harkins.[47]

That the hemoconcentration of the circulating blood in burns is due to a loss of plasma into the tissues at the burned site has been clearly shown by a number of investigators. Underhill and Fisk,[122] and Beard and Blalock,[6] showed that the composition of the edema fluid that escapes from the blood after burns is essentially that of plasma. The fluid shift from the circulating blood to the tissues at the site of the burn was demonstrated and quantitated by Blalock[8] experimentally, by burning one side of the animal and then bisecting the animal and comparing the weight of the two sides. In a series of burned dogs, the edema fluid averaged 3.34 per cent of the body weight, which is about one-half of the plasma volume. In plasmapheresis experiments Blalock found that 3.5 per cent of the body weight of plasma removed would kill the animals. These experiments were confirmed by Harkins,[47, 50] who, in addition, placed unilaterally burned animals on a tipping apparatus so that as the burned side grew heavier a kymographic tracing measured the weight shift and recorded the local accumulation of fluid in experimental burns. Accompanying the collection of fluid was a simultaneous increase in the percentage of hemoglobin and in the hematocrit readings. That the blood volume is reduced by as much as 50 per cent in experimental burns was shown by Schievers,[107] who attributed this mainly to transudation of plasma. Stasis due to low blood volume was thought to be important in the development of Curling's ulcer by Brooks and Blalock.[12]

It should be noted here that, whereas in human beings there is, in addition to the local swelling of the burned area, an external loss of fluid containing protein in the form of exudate, in dogs, experimentally burned, the latter factor is not present because the skin of a dog does not "weep"; the fluid shift in dogs from the circulating blood is entirely into the edematous burned area.

Hemoconcentration, it is well known, may occur in conditions other than burns. Davis[28, 29] produced hemoconcentration experimentally by causing a fluid shift of the water compartment of the blood to the subcutaneous area. He studied acute shock in anesthetized dogs by injecting hypertonic salt solution subcutaneously. The injected area became edematous and changes similar to burns occurred. The high dosage used resulted in shock and death of the animals.

Increased concentration of the cellular elements of the blood concomitant with an increased blood volume is present in patients with polycythemia vera. It is pertinent to note that the incidence of gastric and/or duodenal ulcer in patients with polycythemia vera (8 per cent) is higher than in routine patients, according to Wilbur and Ochsner.[135] One patient with all the clinical findings of polycythemia vera (hemoconcentration, plethora, and increased blood volume) has been studied at the University of Minnesota Hospitals. After numerous venesections for this disease, the patient was subjected to total gastrectomy, following which all these characteristic findings fell within normal limits.[40]

Wood and Blalock[139] studied the effects of experimental uncomplicated hemoconcentration, an increased concentration of the blood not accompanied by changes in blood volume or by shock. They removed whole blood daily (2 per cent of body weight or one-fifth of the total blood volume) from twenty-one dogs, and reinjected red blood cells of equal volume from a compatible donor until uncomplicated hemoconcentration occurred (in eight to eleven days). In these animals they noted several peptic ulcers, and vascular engorgement of the viscera was a fairly common finding.

Related theories of the genesis of Curling's ulcer are found in the literature. In 1871, Falk[32] stated that an inhibition of gastrointestinal circulation, accounting for the ulcer, results from a depressed action of the heart. Kraus, in 1863, Klebs, in 1860, and Jez, in 1900,[74] all attributed the ulcers to stasis in a circumscribed zone with secondary digestion. Pack and Davis[95] believed that hemoconcentration acted in a novel manner in the genesis of Curling's ulcer; they postulated that the bile may become so inspissated because of the marked blood concentration that it does not flow readily, the absence of bile being a factor in the etiology of ulcer.

Theories of Thromboembolic Phenomena.—According to Pack,[94] a predisposition to thrombosis exists in burns and scalds because of the leucocytic disintegration, the venous stasis, and the viscidity of the concentrated blood.

Many investigators (as early as Baradue,[3] in 1863) have attributed a goodly portion of the visceral pathology in burns to minute capillary thrombi. Those who have suggested capillary thrombosis as the etiological factor in the genesis of Curling's ulcer include Sonnenburg, 1879; Leotta, 1904; and Ewald, 1912.[110] In discussing the visceral changes in burns, Pack[94] stated that he believed that thrombosis is not nearly as important a factor as thick viscid blood.

Billroth,[7] in 1867, was one of the first to attribute the ulcers to an embolic (septic) process. He believed that the infarcted area sloughed away. Ericksen,[31] in 1895, Broadbent,[11] in 1908, and Stengel,[112] in 1926, among others, supported the theory of capillary embolism with secondary digestion. Moynihan[90] in his book, in 1912, apparently in agreement with Billroth, believed that septic emboli were the cause of Curling's ulcer.

Kabat,[70] experimenting with scalds in cats, showed that heated plasma of both cats and human beings formed a precipitate which acted as capillary emboli when injected. He noted a perforated gastric ulcer in a cat so injected. Homogenization rendered the precipitate innocuous.

Fat embolism was reported by Carrara[14] to occur in 44 per cent of individuals with burns coming to autopsy, and was suggested as an important factor in the genesis of Curling's ulcer by Salvioli,[106] in 1891, and Merkel,[89] in 1914.

The role of fat embolism in the development of gastroduodenal ulcer after bone trauma, clinical and experimental, has been reported recently.[41]

Toxin Theories.—Theories relating to a toxin or toxic products in the genesis of Curling's ulcer are numerous. There is no conclusive evidence that a toxin is present in burned patients or animals; neither is there any unanimity of opinion as to the nature or chemical composition of the toxin, if one occurs, nor its site of origin, elaboration, mode of transfer, or ultimate effects on the organism.

One of the first to postulate a toxin in the genesis of Curling's ulcer was Catiano,[16] in 1882, who believed that hydrocyanic acid forms in the skin by the following process: since sweat contains formic acid, the neutralization of this acid on the skin by ammonium hydroxide forms the very soluble ammonium formate salt. When this salt is heated, it loses water and becomes hydrocyanic acid. This substance or toxin, reaching the intestinal wall, causes a reduction in its natural alkalinity, allowing digestion of the mucosa to ensue. The irritant action of noxious bile has been incriminated. Mendel,[88] in 1870, believed that a pathologic modification of the bile with resultant inflammation was a factor. Hunter,[68] in 1890, attributed the ulcers to the action of noxious bile due to its content of the presumptive toxin secreted by the liver. Fenwick and Fenwick[34] repeated some of Hunter's experiments on dogs and found ulcers even after ligation of the common bile duct, which throws doubt on Hunter's conclusion. Furthermore, as pointed out by DaCosta,[26] typical duodenal ulcers following burns occur well above the ampulla of Vater. Harris[56] believed that the action of the toxin, carried by the blood and not the bile, produces focal necrosis and hemorrhage in the duodenal mucosa, which is transformed into ulcers by the digestive action of the pancreatic juice.

Toxin Theories Relating to Histamine as the Toxin, Excessive Gastric Acidity, and Gastric Hypersecretion.—It is well known that histamine is found in many normal tissues of the body and it has been suggested as the toxin in burns.

Because of the unique action of histamine as a specific stimulant to gastric secretion of acid, one would expect to find corroborative evidence in reported studies of gastric acidity in burns, if histamine, as the toxin of burns, is present in the blood following thermal trauma. This type of information would be directly related to the genesis of Curling's ulcer inasmuch as hyperacidity is

universally considered the determining factor in ulceration over and above oft-hypothesized predisposing states. Also relevant and obvious is the profound influence of histamine, as a beeswax mixture, on the experimental production of gastroduodenal ulcer in animals, as shown by Hay and associates.[60] Such studies, with contradictory results, have been carried out: Necheles and Olson[91] studied gastric secretion in dogs with isolated gastrostomized stomachs, following torch burns to the hind legs of the animal. They noted that such burns augmented gastric secretion if, however, infusions of fluid were given at the time of study. Hartman[58] was unable to confirm these findings and found that both the free hydrochloric acid and the total acid were, if anything, reduced following burns. Wilson[138] studied patients afflicted with burns and showed by gastric analyses that there is no excessive gastric acidity.

Inasmuch as the histamine-in-beeswax technique used as a tool to provoke maximum gastric secretion has been repeatedly used and referred to in this study, it should be noted here that (1) in rabbits bona fide ulcers cannot be produced with histamine alone,[60] and (2) in dogs, Hay and his associates[60] noted that forty days were necessary to produce ulcer with regularity in all dogs injected. In Hay's series of twelve dogs, twenty-three days was the average time for ulcer production employing the histamine-in-beeswax technique. Any ulcer noted within four or five days is said to be accountable to a predisposing condition or abetting influence to the histamine-provoked ulcer in dogs. In addition, it is well documented by Lannin[75] that a three-quarter gastric resection, employing a short proximal duodenal loop, completely and regularly protects against the histamine-provoked ulcer in dogs even after forty daily injections of histamine-in-beeswax mixture. In human beings this operation, as advocated by Wangensteen,[126] has mirrored the experimental protection found in the laboratory, as shown in an extensive report of over 400 patients by Gaviser,[44] in which the incidence of recurrent ulceration following this operation is less than 1 per cent.

Related to the toxin theory in the genesis of Curling's ulcer is the theory of infection or sepsis; a toxin, bacterial or septic emboli—all of which claim many followers.

The association of infection and burns has always been a predominant one and its importance is reflected, in the main, by the numerous methods of local treatment designed to combat or control bacterial growth. Indeed, one definition of a burn is "an infected wound produced by heat." Secondary pyogenic infection of the burned area however, is, in reality, the most common complication of burns and scalds. A majority of severe burn cases do not have marked infection during the first twenty-four to forty-eight hours, which is the time when increased blood concentration (with or without shock), low cardiac output, and low blood volume occur.

The frequent association of infection in the burned area with subsequent development of a duodenal ulcer has been repeatedly noted. Infection may act by way of an embolic phenomenon or by means of toxin production which acts directly on the duodenum and/or adrenal glands. As early as 1855, Gibbon[45] believed ulcers are due to inflammation which attacks the duodenum because

it is one of the most vascular of organs, but Billroth,[7] in 1867, was one of the first to notice the connection between sepsis following thermal injuries and duodenal ulcers. He attributed the development of the ulcers to a process of septic embolism, the infarcted area sloughing away to form the ulcer. Septic emboli were also indicted in the genesis of duodenal ulcer following burns of the abdominal wall by Stallard and Borman,[111] who explained the ulcers to be due to the passage of septic emboli from the burned area, by way of the vascular or lymphatic channels in the ligamentum teres, to produce infarction of the duodenal wall. Perry and Shaw[97] were ardent advocates of the septic theory and called attention in their extensive report in 1893 to the similarity, in cases with duodenal ulcer, of burns and septic conditions other than burns. Harkins,[53] in his extensive collection of cases in 1938, pointed out the relation to sepsis, showing that sepsis was present in all twenty-four cases of Curling's ulcer in which pertinent data were given.

The role of sepsis in the mechanism of the development of gastroduodenal ulceration following burns was studied experimentally by Hartman.[58] He used live steam to produce a 50 to 60 per cent burn in dogs, and, in a period extending up to thirteen days, observed ulcerations in the duodenum and stomach in 63.3 per cent of the animals. In another series in which tanning agents were employed as a lenitive to infection, the incidence of spontaneous ulcer was 6.6 per cent. In a further study by Hartman[59] in which dogs, so burned, were given penicillin, 10 to 50,000 units intramuscularly once daily, the incidence was 23 per cent. The incidence of the occurrence of ulceration in burns is decreased by such chemotherapy, but not prevented completely. Leube[77] believed that accumulation of waste products in the blood was important in the genesis of Curling's ulcer by inhibiting the force of the circulation.

Theories Relating to Shock.—Upon superficial examination it may seem superfluous to segregate "shock" as an individual classification in the genesis of Curling's ulcer. Theoretically, the development of shock, and similarly, the development of ulcer in burns may be due to a number of factors—nervous, adrenal, toxic, bacterial, physical, and so on, but practically, a fine differentiation should be made as to whether shock, per se, regardless of its own etiology, is a factor or the factor responsible for the development of Curling's ulcer.

In 1881, Hills,[65] in reporting a duodenal ulcer which occurred in a patient fatally scalded, claimed the ulcer to be due to "shock" to the stomach, since shock exists in burns. It is commonly acknowledged that shock, primary and/or secondary, may be present in trauma, thermal or otherwise; however, it is difficult to ascertain from the literature the frequency with which this factor attends burns.

Blalock[8] produced experimental shock by means of burns, and Brooks and Blalock,[12] in experimental studies of the etiology of traumatic shock, noted duodenal congestion, necrosis, and bleeding in the shock of slow hemorrhage, and following trauma to the extremities. The hematocrit was not elevated in all of the shock experiments and intestinal congestion was not a constant finding. Hemoconcentration may occur without evidence of shock, and vice versa.

The Adrenal Factor.—Pathologic changes in the adrenal glands at necropsy on patients succumbing from extensive burns have been frequently noted. Weiskotten,[130] in an intensive study of ten necropsies of burned patients, found adrenal hemorrhage and necrosis. That these changes also occur in hemorrhage and trauma to muscles, indicating that they are not specific to burns, has been shown by Brooks and Blalock.[12] In Harkins' extensive review of the literature on Curling's ulcer,[53] only three cases out of ninety-four collected had adrenal hemorrhages, which indicates that the relationship may be concomitant rather than causal. Furthermore, several instances[52] of adrenal change following burns without associated Curling's ulcer have been reported.

The experimental work of McLaughlin[86] has given impetus to the adrenal theory in the etiology of Curling's ulcer. He produced graduated adrenal damage not sufficiently extensive to cause gross adrenal insufficiency in dogs by applying a high frequency coagulation current to the adrenals in two stages. He noted that when the animals were sacrificed one to four weeks later, ulceration in the duodenum and small intestine was present in seventeen of twenty-one dogs. Gastric analyses in three dogs tested revealed normal acidity. Adrenal insufficiency due to adrenalectomy may produce changes similar to burns. Mann[84] noted ulcers in 40 of 60 adrenalectomized dogs, and Stewart and Rogoff[113] reported them in 48 of 118 dogs, all of which showed intestinal congestion. That adrenal insufficiency, produced both by McLaughlin's method and by adrenalectomy, aids in the development of the histamine-in-beeswax provoked ulcer in a series of thirty dogs has been shown.[43] Dalton and Masson[27] showed that the blood picture after adrenalectomy in rats is concomitant with hemoconcentration. A decrease in blood sugar after adrenalectomy in animals has been noted by Britton.[10]

DESCRIPTION OF METHODS, EXPERIMENTS, AND RESULTS

General Considerations

This study was carried out experimentally on the laboratory animals, dogs and rabbits. Physiologic and pathologic alterations in these animals following experimental burns and other correlating conditions were given special attention.

Standardization of the experiments was done first; this consisted of establishing a standard method of experimental burns in the animals and determining the rate and time of occurrence of gastroduodenal ulceration subsequent to the burn, both with and without the maximum stimulus to gastric acid secretion by histamine injection. The standard rate and time of occurrence of gastroduodenal ulceration due to histamine-in-beeswax administered alone is known by previous experimentation and by control experiments in this study.

Following the standardization, series of experiments were carried out to investigate the more commonly accepted theories as to the etiology of Curling's ulcer. The validity of each such theory was tested directly or indirectly against the standards set forth, that is, by determining whether either an acceleration or a prevention of a standard incidence or time of occurrence of gastroduodenal ulceration occurs. In each series of experiments one condition only was altered, or one physiologic variant was especially studied. Data obtained from some

series of experiments, however, were included in other series when the information was pertinent; indicated control experiments were carried out in each series. Several series of correlating experiments in animals not subjected to burns were carried out to furnish contributing and substantiating evidence.

A majority of animals in all experiments were subjected (while completely anesthetized) to burns which consisted of immersion in water at 100° C., the body surface area and period of exposure determined in the standardization experiments. Immersion was found to be a satisfactory method of producing burns in that (1) accurate standardization is possible, (2) the tissue is not broken at the time of the burn, and (3) no added factor of pressure on the tissue is present. All animals subjected to burns were anesthetized with sodium pentobarbital, 15 mg. per pound body weight, administered intravenously. In all instances the anesthesia was more than adequate to obviate pain or any suggestion of discomfort on the part of the animal during the burning process; occasionally, Demerol, 50 mg. intramuscularly, was used in addition. Considerate care was given these animals at all times to allay pain or discomfort. The hair of the animal was closely clipped prior to scalding.

A number of animals received, in addition to the burn, daily intramuscular injections of histamine-in-beeswax mixture prepared after the method of Code and Varco[19] (30 mg. base in the dog, and 15 mg. base in the rabbit). The first histamine injection was given two hours prior to the burn and then daily each evening, after which the food pans were removed and no more food was given until the following morning. The dogs were fasted for eighteen hours before each experiment. Water intake was allowed up to 250 c.c. per day in all dogs. No restriction of food intake was exercised in the instance of the rabbits.

Blood studies were carried out on a large number of the experimental dogs; three determinations were made before the burn for the average of normal values, and serial determinations were carried out after the burn. The following determinations were made in the pertinent series of experiments: hemoglobin (alkaline hematin method); erythrocyte count; specific gravity of whole blood and plasma (copper sulfate method of Phillips, Van Slyke, and others); blood urea nitrogen (Karr's method); plasma and blood volumes (Gibson and Evan's method); venous clotting time (Lee-White method); and prothrombin time (Quick's method). In most instances rectal temperatures were taken at intervals in the dogs.

The animals were sacrificed by injection of an overdose of barbiturate from four hours to fourteen days following the burn, and to a large extent the time of sacrifice was determined by the occurrence of spontaneous hematemesis, melena, or extreme weakness. In all animals sections of stomach, duodenum, brain, liver, kidney, lung, adrenal, and the burned area were obtained for microscopic observations.

The results of the standardization experiments previously reported in detail[38] (1946), show that dogs receiving daily histamine-in-beeswax injections alone do not present gastroduodenal ulceration within five days, whereas in dogs receiving a superficial burn in addition to histamine injections, the incidence of ulceration is 100 per cent within five days, when the burn extends to 40 per cent of the

body area. When the burn involves 15 per cent of the body surface the incidence of definite ulcers is 66.6 per cent; the incidence of ulcer and/or erosion is 100 per cent within five days. However, the incidence of ulceration in dogs subjected to burns without histamine administration was two of eleven dogs, or 18.2 per cent, indicating that pure Curling's ulcers can be experimentally produced in dogs. The 100 per cent incidence of ulcers in dogs subjected to a 40 per cent cutaneous burn with histamine administration within as little as twenty-four hours affords a standard and uniform tool with which to measure the effect of

Fig. 1.—Congestion, bleeding duodenal ulcers, and gastric petechiae in Dog 15, nine days after a 15 per cent, third degree burn under anesthesia, without histamine administration.

various etiological factors in subsequent experiments. Perhaps the most notable finding in this, the first group of experiments, is the observation that gastrointestinal congestion is a common finding in burned animals, and is a constant finding in burned animals in which ulcers are produced. The relationship of the associated mucosal congestion to the various etiological factors is noted in subsequent experiments. Added evidence that superficial burns are a strong force in the provocation of the histamine ulcer was shown in the fact that ulcers were produced in rabbits, experimental animals which have been shown to be refractory to ulcer produced by histamine-in-beeswax administration alone.

Studies as to Genesis

Hemoconcentration Factor.—Evidence to show that gastrointestinal congestion associated with gastroduodenal ulceration is directly related to hemoconcentration occurring in the burned animal is presented in the results of the following experiments utilizing forty-one dogs in three series (presented in part previously[39]):

Series I (see Table I). Twelve of the fourteen dogs subjected to 40 per cent burns accompanied by histamine administration developed increased concentration of the blood. All twelve dogs demonstrated marked congestion of the mucous membrane of the stomach and duodenum. Nine of these twelve dogs were sacrificed twenty-four hours or more after the burn and showed definite ulcers, five bleeding and two perforated. Three of the twelve dogs were sacrificed at four, six, and eighteen hours after the burn, the latter showing, in addition to the congestion, marked diffuse bleeding from the surface of the gastric and duodenal mucosa. The two dogs which failed to develop increased concentration of the blood demonstrated no gastric or duodenal pathology in one and four days.

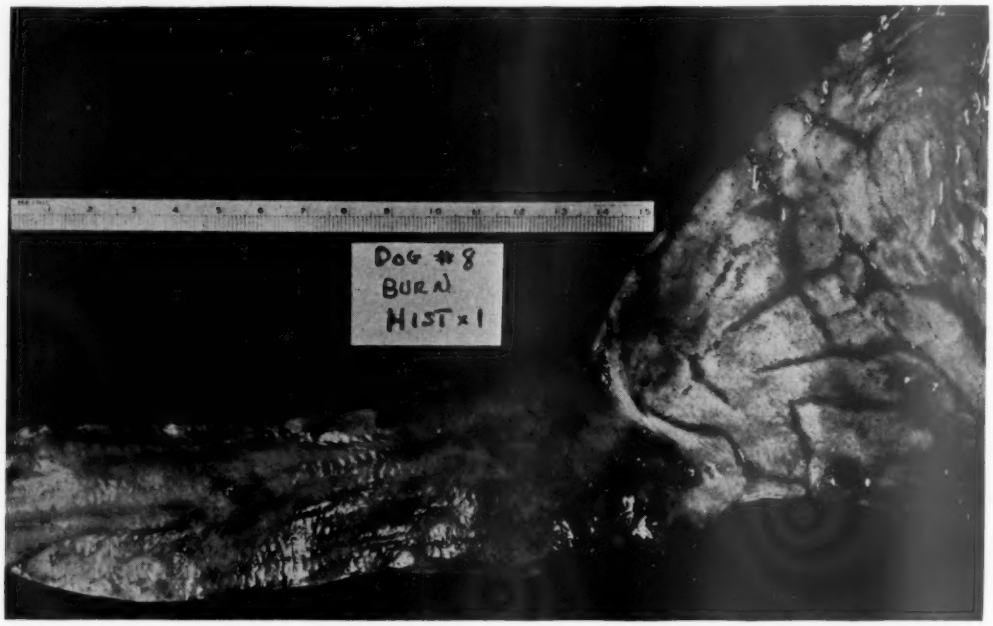

Fig. 2.—Congestion, bleeding duodenal ulcers, and hemorrhagic gastritis in Dog 8 dying of exsanguination within twenty-four hours after a 40 per cent, third degree burn and one injection of histamine-in-beeswax mixture.

Series II (see Table II). Eleven of the twelve dogs subjected to 40 per cent burns without administration of histamine-in-beeswax developed increased concentration of the blood and demonstrated congestion of the gastrointestinal mucosa in four hours to six days. Five of these dogs showed, in addition to congestion, bleeding petechial gastric ulcers, duodenal erosions, and antral bleeding points. One (Dog 28) failed to develop increased concentration of the blood and demonstrated no gastric or duodenal pathology in four days.

Series III (see Table III). In this series, an attempt to prevent hemoconcentration was carried out by intravenous infusions of human dried plasma at a rate regulated by serial blood studies. Of the ten dogs subjected to 40 per cent burns accompanied by histamine-in-beeswax administration, in which an attempt at prevention of the hemoconcentration in burns was made, seven dogs were well controlled throughout the entire duration of the experiment, two dogs were partially controlled, and one dog was overtreated. The seven dogs in which

TABLE I. INVESTIGATION OF THE HEMOCONCENTRATION FACTOR

Dogs Subjected to 40 Per Cent Burn Accompanied by Daily Administration of Histamine-in-Beeswax (30 Milligram Base); Not Treated With Intravenous Infusion

DOG NUMBER	WEIGHT IN POUNDS	BURN		NUMBER JECTIONS OF HISTA-	HEMATOCRIT CHANGE		RESULTS	REMARKS
		PER CENT	SECONDS	MINE IN-	INITIAL	FINAL		
23	29	40	10	4	40	41	No congestion, erosion, or ulcer	Died, anorexia
24	32	40	10	5	44	55	Congestion; duodenal ulcers, one perforated	Died, peritonitis
25	22	40	10	3	42	53	Congestion; pyloric and duodenal ulcers	Died in 3 days
36	17	40	15	1	49	56	Congestion; small pyloric ulcer; many bleeding points	Sacrificed, 24 hours
37	22	40	15	2	43	65	Congestion; bleeding pyloric ulcer; two large duodenal ulcers	Sacrificed, 48 hours
38	24	40	15	2	50	61	Congestion; pyloric-duodenal ulcer; bleeding small fundic ulcers	Died in 2 days, melena
39	22	40	15	2	30	41	Congestion; large duodenal ulcers, one perforated; fundic ulcers	Died, peritonitis
40	24	40	15	2	50	55	Congestion; three large duodenal ulcers; one large gastric ulcer; many small bleeding ulcers	Sacrificed, melena
42	15	40	15	1	40	57	Congestion; marked bleeding in stomach and duodenum	Sacrificed, 18 hours
44	20	40	15	1	49	72	Intense congestion	Sacrificed, 4 hours
45	26	40	15	3	47	56	Congestion; bleeding antral ulcer	Died in 3 days
50	22		10	1	42	42	No congestion, erosion, or ulcer	Sacrificed, 24 hours
51	36	40	10	1	49	54	Congestion only	Sacrificed, 6 hours
52	31	40	15	1	40	53	Congestion; large duodenal ulcer; many petechial gastric ulcers	Sacrificed, 24 hours

TABLE II. INVESTIGATION OF THE HEMOCONCENTRATION FACTOR

Dogs Subjected to 40 Per Cent Burn; No Histamine Administration; Not Treated With Intravenous Infusion

DOG NUMBER	WEIGHT IN POUNDS	BURN		NUMBER OF HISTAMINE INJECTIONS	HEMATOCRIT CHANGE		RESULTS	REMARKS
		PER CENT	SECONDS		INITIAL	FINAL		
26	26	40	10	0	50	56	Bleeding petechial gastric ulcers, congestion	Sacrificed, 6 days
27	31	40	10	0	45	57	Hemorrhagic gastritis, duodenitis; antral bleeding points; marked congestion	Died in 2 days
28	15	40	10	0	59	60	Essentially negative	Died in 4 days
29	24	40	15	0	48	59	Congestion only	Sacrificed, 5 days
30	30	40	15	0	45	56	Congestion only	Died in 5 days
58	32	40	15	0	46	67	Marked congestion	Sacrificed, 20 hours
59	34	40	15	0	57	76	Marked congestion	Sacrificed, 24 hours
60	28	40	15	0	50	61	Marked congestion	Sacrificed, 4 hours
61A	20	40	15	0	51	72	Marked congestion	Exsanguinated in 4 hours
62A	28	40	15	0	47	69	Marked congestion, bleeding duodenal erosions	Exsanguinated in 12 hours
63A	40	40	15	0	47	63	Congestion, antral petechiae, pyloric erosions	Exsanguinated in 24 hours
64A	31	40	15	0	48	69	Congestion, antral petechiae, duodenal erosions	Exsanguinated in 2 days

TABLE III. INVESTIGATION OF THE HEMOCONCENTRATION FACTOR

Dogs Subjected to 40 Per Cent Burn, Accompanied by Histamine-in-Beeswax Administration, Treated by Intravenous Infusion

DOG NUMBER	WEIGHT IN POUNDS	BURN		NUMBER OF HISTAMINE INJECTIONS	CONCENTRATION OF BLOOD	RESULTS	REMARKS
		PER CENT	SECONDS				
43	21	40	15	1	Maintained at normal values	No congestion, erosion, or ulcer	Sacrificed, 18 hours
49	32	40	15	1	Maintained at normal levels	No congestion, erosion, or ulcer	Sacrificed, 24 hours
53	35	40	15	1	Maintained at normal levels	No congestion, erosion, or ulcer	Sacrificed, 24 hours
46	18	40	15	2	Normal except for 18 hours of hemoconcentration	Congestion, lesser curvature ulcers	Sacrificed, 54 hours
47	19	40	15	2	Normal except for 18 hours of hemoconcentration	Congestion, perforated duodenal ulcers	Died, peritonitis, 54 hours
41	22	40	15	1	Overtreated; hemodilution	Pallor, submucosal and mucosal hemorrhage, and erosion of stomach	Died in 16 hours
65	26	40	15	3	Maintained at normal levels	No congestion, erosion, or ulcer	Sacrificed, 72 hours
70	34	40	15	5	Maintained at normal levels	No congestion, erosion, or ulcer	Sacrificed, 5 days
71	36	40	15	3	Maintained at normal levels	No congestion, erosion, or ulcer	Died in 3 days
72	22	40	15	4	Maintained at normal levels	No congestion, erosion, or ulcer	Sacrificed, 4 days
Controls (No burn; histamine plus plasma infusions)							
48	26	0	0	4	Slight hemodilution (not significant)	No congestion, erosion, or ulcer	Sacrificed, 4 days
Controls (No burn; histamine administration)							
1A	32	0	0	5	No significant change	No congestion, erosion, or ulcer	Sacrificed, 5 days
2A	28	0	0	5	No significant change	No congestion, erosion, or ulcer	Sacrificed, 5 days
3A	27	0	0	5	No significant change	No congestion, erosion, or ulcer	Sacrificed, 5 days
4A	22	0	0	5	No significant change	No congestion, erosion, or ulcer	Sacrificed, 5 days

blood concentration values were maintained at normal levels demonstrated no gastric or duodenal pathology when sacrificed in eighteen hours to five days. The two dogs in which normal blood concentration values were maintained, except for a period of eighteen hours out of a total duration of fifty-four hours, demonstrated gastrointestinal congestion, with lesser curvature ulcers and perforated duodenal ulcer, respectively. One dog was overtreated in the first few hours of the experiment so that marked hemodilution occurred. Death occurred in this animal in sixteen hours, presenting pallor of the stomach with several areas of mucosal and submucosal hemorrhage and erosions.

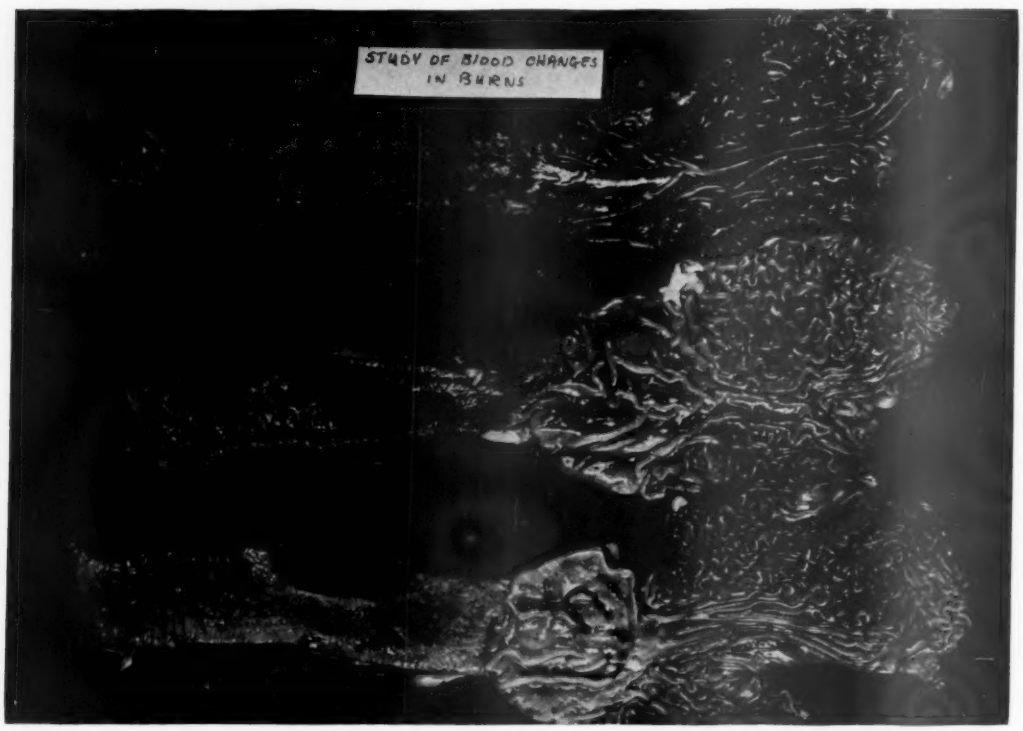

Fig. 3.—Stomachs and duodenums of dogs subjected to 40 per cent, third degree burns, accompanied by histamine-in-beeswax administration.

Top: Dog 42 (Table I, untreated hemoconcentration). Marked congestion with diffuse bleeding from the mucosa of stomach and duodenum.

Middle: Dog 43 (Table III, adequately treated with intravenous infusion of plasma to prevent hemoconcentration). No congestion, erosion or ulcer of stomach and duodenum.

Bottom: Dog 41 (Table III, overtreated with plasma infusions producing hemodilution). Pallor with mucosal and submucosal hemorrhages and erosions of stomach.

Microscopic examination of the viscera of the animals developing hemoconcentration showed marked vascular congestion; of the animals in which hemoconcentration did not take place or was prevented, no significant findings were noted.

Four dogs receiving daily intramuscular injections of histamine-in-beeswax for five days developed no hemoconcentration and no gastrointestinal abnormality. The additional control dog receiving histamine injections and plasma infusions without a burn developed slight but insignificant hemodilution and no gastrointestinal pathology.

Corroborative evidence to the data just given from animals not subjected to burns is given in the following three series of experiments.

Series IV and V. In these series of experiments hypertonic salt solution (10 c.c. of 25 per cent sodium chloride per kilogram of body weight) was injected subcutaneously into twenty-four dogs to transfer the water compartment of the blood to the site of injection, thus tending to produce a type of hemoconcentration. In those dogs in which significant hemoconcentration was produced by this method, gastrointestinal congestion was found which led to erosion or ulceration when histamine administration for less than five days was added.

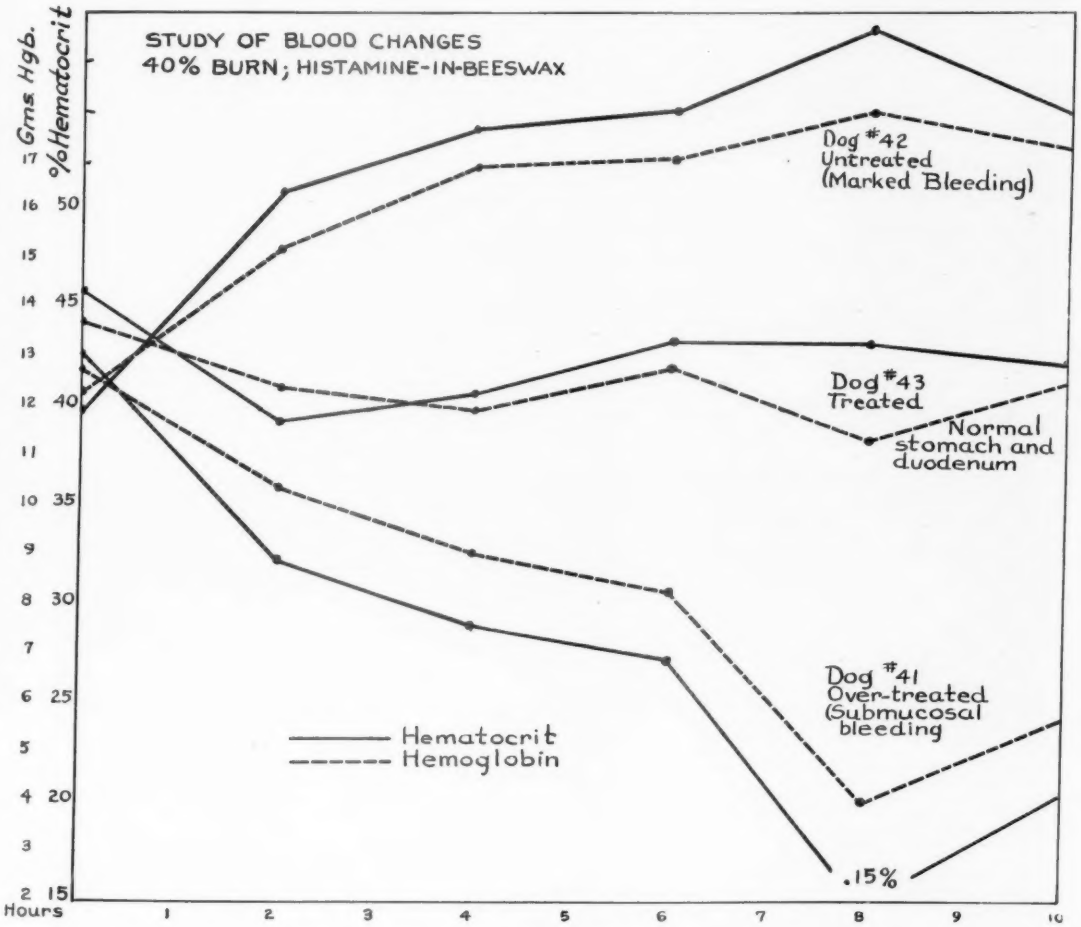

Fig. 4.—Hemoglobin and hematocrit changes in dogs (see Fig. 3) subjected to 40 per cent, third degree burns, accompanied by histamine-in-beeswax administration (Dog 42 from Table I; Dogs 43 and 41 from Table III).

Series VI. An uncomplicated hemoconcentration was experimentally accomplished in four of eight dogs subjected to repeated extraction of plasma from withdrawn blood, and reinjection of a thick solution of the cellular elements of the blood to maintain a normal blood volume with increasing cellular concentration of the blood. These four dogs developed mucosal congestion, erosions, and ulcers after two and three histamine injections. No gastrointestinal pathology

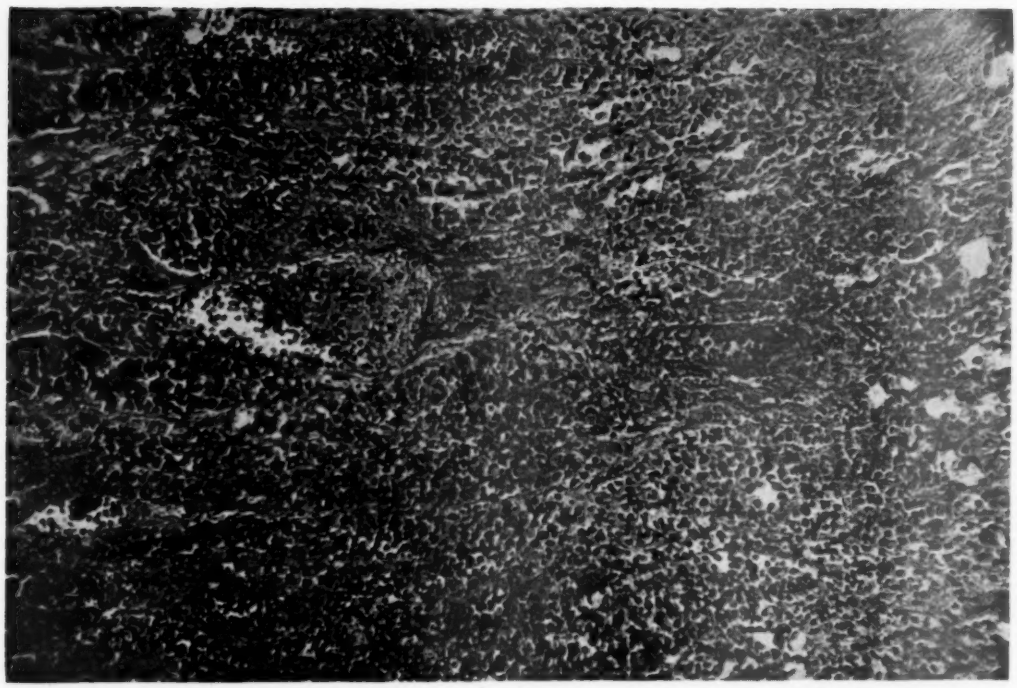

Fig. 5.—Photomicrograph (high power) of gastric mucosa of Dog 42 (see Figs. 3 and 4, Table I) illustrating the marked vascular engorgement, extravasation, and superficial necrosis producing mucosal congestion and bleeding after extensive burns. The sacrificed animal had developed marked untreated hemoconcentration.

Fig. 6.—Photomicrograph (high power) of gastrointestinal mucosa of Dog 43 (see Figs. 3 and 4, Table III) illustrating mucosa without vascular engorgement, following an extensive burn in which hemoconcentration was prevented by intravenous infusion of plasma.

was noted in the dogs which failed to develop hemoconcentration by this method, whether or not histamine was administered. There was no thrombosis or embolism evident in any of the animals.

Thromboembolic Factors.—Series VII (see Table IV). Inasmuch as it is believed by some investigators that thromboembolic states, which may be present in burns, occlude end vessels in the stomach and duodenum in the genesis of Curling's ulcer, the following experiments and studies were set up to explore the validity of such statements.

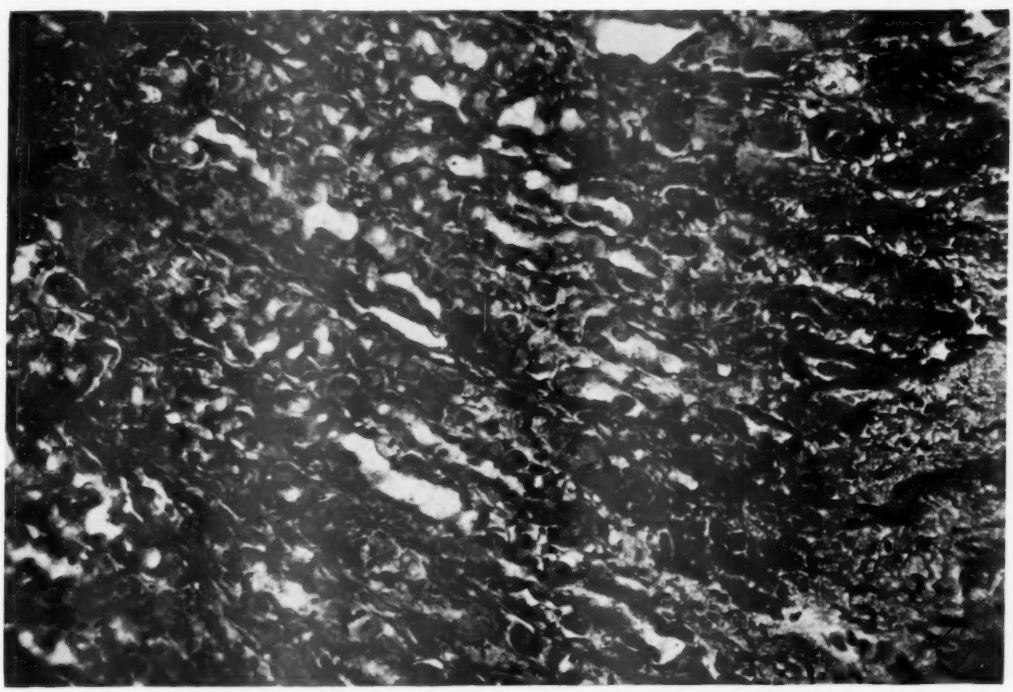

Fig. 7.—Photomicrograph of gastric mucosa of Dog 41 (see Figs. 3 and 4, Table III) illustrating the effect of marked hemodilution produced by overtreatment with infusions of plasma following an extensive burn. The vascular spaces are practically devoid of the cellular elements of the blood, producing an ischemia to the point of superficial mucosal necrosis.

Fat Embolism: Study of the microscopic sections stained with sudan III of stomach, duodenum, brain, liver, kidney, lungs, and adrenals taken from nineteen burned dogs and ten burned rabbits revealed not a single suggestion of fat emboli. The base of ulcers studied showed no evidence of fat emboli.

Toxin Factors.—

Transfer-circulation experiments: Series VIII. In this series of experiments the blood (with presumably circulating toxin) from burned donor dogs, exsanguinated at varying lengths of time, was transferred into normal recipient dogs in which blood concentration was maintained unaltered as shown in Table V. All four donor dogs developed hemoconcentration and gastrointestinal congestion at four, twelve, twenty-four, and forty-eight hours, with erosions and bleeding points after twelve hours without histamine administration. All four recipient dogs in which blood concentrations remained unchanged failed to develop gastro-

TABLE IV. INVESTIGATION OF THE THROMBOEMBOLIC FACTOR

Dogs Subjected to Extensive Burns and Anticoagulant Therapy, in Addition to Histamine-in-Beeswax Administration

NUMBER DOG	WEIGHT IN POUNDS	BURN		NUMBER OF HISTAMINE INJECTIONS	ANTI-COAGULANT THERAPY*	PROTHROMBIN TIME (SECONDS)	VENOUS CLOTTING TIME	HEMATOCRIT CHANGE		RESULTS
		PER CENT	SECONDS					INITIAL	FINAL	
18	33	15	20	2	D	65/14	30′ 15″	45	58	Congestion; two bleeding pyloric ulcers
22	27	15	20	1	H		Over 3 hours	50	61	Congestion; bleeding antral erosion
23	29	40	10	4	H & D	36/13	Over 3 hours	40	41	No congestion, erosion, or ulcer
24	32	40	10	5	H & D	45/13	Over 3 hours	44	55	Congestion; perforated duodenal ulcers
32	29	40	15	1	H & D	Over 15′/9	29′ 5″	39	58	Extreme congestion and petechiae in 8 hours
33	35	40	15	1	D	135/9	20′ 45″	51	67	Extreme congestion in 5 hours; profuse bleeding petechiae in stomach and duodenum
Controls										
34	28	0	0	4	D	Over 15′/9	30′ 5″	34	36	No congestion, erosion, or ulcer
21	32	15	20	0	H & D	55/14	Over 3 hours	42	39	No congestion, erosion, or ulcer in 14 days
35	28	40	10	1	None	5/9	6′ 40″	46	57	Congestion, gastric ulcer, and esophageal petechiae in four days

*H, Heparin therapy (50 mg. intravenously every four hours for two days).
D, Dicumarol therapy (100 mg. powder by orogastric tube daily beginning six days prior to burn).

TABLE V. INVESTIGATION OF THE TOXIC FACTOR

Donor Dogs Subjected to 40 Per Cent Burns, Exsanguinated at Intervals; Recipient Dogs Received No Burn and Were Sacrificed After Five Days of Histamine Administration

DOG NUMBER	WEIGHT IN POUNDS	DONOR OR RECIPIENT DOGS	TIME OF BLOOD TRANSFERS AFTER BURN (HOURS)	AMOUNT OF BLOOD WITHDRAWN	AMOUNT OF DONOR BLOOD PLUS SALINE INFUSED	NUMBER OF HISTAMINE INJECTIONS	HEMATOCRIT CHANGE		RESULTS
							INITIAL	FINAL	
61A	20	Donor	4	350		0	51	72	Intense gastrointesinal congestion
61B	20	Recipient	(4)	300	350 200 300	5	38	40	No congestion, erosion, or ulcer
62A	28	Donor	12	450		0	47	69	Intense congestion with antral petechial and bleeding duodenal erosions
62B	31	Recipient	(12)	550	450 250	5	53	51	No congestion, erosion, or ulcer
63A	40	Donor	24	850		0	47	63	Congestion with antral petechial and pyloric erosion
63B	36	Recipient	(24)	900	850 300	5	51	50	No congestion, erosion, or ulcer
64A	31	Donor	48	800		0	48	69	Congestion with antral petechial and duodenal erosions
64B	33	Recipient	(48)	850	800 300	5	44	40	No congestion, erosion, or ulcer

intestinal congestion, erosion, or ulcer, even in the face of the maximal ulcer-provoking stimulus of daily histamine-in-beeswax administration for five days.

Toxin theories relating to histamine and gastric acidity: Series IX. If the toxin elaborated in the burned area and released into the systemic circulation is histamine or a histamine-like substance, it should be possible to detect its presence in burned animals by studies of gastric secretion before and after the burn.

Accordingly, four dogs possessing gastric secretory pouches (two innervated and two denervated) were subjected to 15 per cent, third degree burns, and studies of gastric secretion were carried out before and after the burn (see Table VI). A uniform but slight reduction in secretory volume, with no significant alteration of gastric acidity values, was noted when studied immediately after, and three and four days after the burn, indicating that histamine, as the toxin, does not appear to be significantly present in the blood of the dog following an extensive burn.

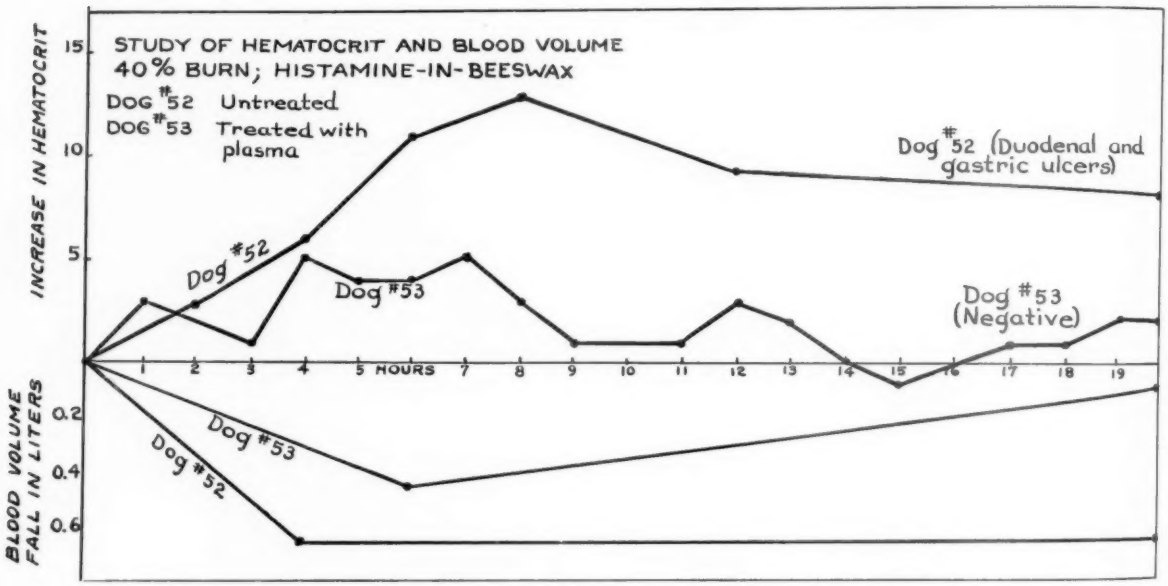

Fig. 8.—Hematocrit and blood volume changes in two dogs (Dogs 52 and 53, Tables I and III) subjected to 40 per cent, third degree burns accompanied by histamine-in-beeswax administration demonstrating the protection afforded by adequate control of the blood concentration and blood volume by intravenous infusions of plasma as compared to the untreated animal.

Series X (see Table VII). Four dogs having had a subtotal short loop gastric resection six to eighteen months previously were subjected to 40 per cent burns in addition to histamine-in-beeswax administration. All four dogs developed significant increased concentration of the blood and mucosal congestion; two dogs with 75 per cent resections developed a stomal erosion and a stomal ulcer, respectively. The remaining two dogs, which failed to show erosion or ulceration when sacrificed on the second and fifth days, had had 80 and 90 per cent gastrectomies. Thus, a reduction of available gastric acidity by subtotal gastrectomy reduces the expected incidence of erosion and ulceration, but not that of mucosal congestion.

TABLE VI. INVESTIGATION OF TOXIN, HISTAMINE, AND HYPERSECRETION FACTORS

Studies of Gastric Secretion in Pouch Dogs Subjected to Third Degree Burns

DOG NUMBER	WEIGHT IN POUNDS	BURN		AVERAGE VALUES OF POUCH SECRETION PER 1 HOUR				REMARKS
				VOLUME (C.C.)		FREE ACIDITY (DEGREES)		
		PER CENT	SECONDS	BEFORE	AFTER	BEFORE	AFTER	
369 H*	45	15	20	3	2.5	30	35	Congestion of stomach and pouch; sacrificed, 6 days
142 H	39	15	20	2	1	20	20	Congestion of stomach and pouch; sacrificed, 6 days
147 P	35	15	20	4	2	35	30	Congestion of stomach and pouch; sacrificed, 6 days
287 P	42	15	20	4	2.5	15	10	Congestion of stomach and pouch; sacrificed, 6 days

*H, Heidenhain pouch (denervated).
P, Pavlov pouch (innervated).

TABLE VII. INVESTIGATION OF THE TOXIN, HISTAMINE, AND GASTRIC ACIDITY FACTORS

Dogs With Subtotal Gastric Resection, With Short Proximal Loop, Subjected to Extensive Superficial Burns and Daily Administration of Histamine-in-Beeswax Mixture (30 mg. Base)

DOG NUMBER	WEIGHT IN POUNDS	BURN		NUMBER OF HISTAMINE INJECTIONS	PER CENT GASTRIC RESECTION	HEMATOCRIT CHANGE		RESULTS	REMARKS
		PER CENT	SECONDS			INITIAL	FINAL		
66	32	40	15	5	75	35	49	Congestion; large (2.5 cm.) ulcer at efferent stoma	Sacrificed, 5 days
67	23	40	15	2	80	33	50	Congestion; no erosion or ulcer	Sacrificed, 2 days
68	35	40	15	5	90	40	54	Congestion; no erosion or ulcer	Sacrificed, 5 days
69	30	40	15	5	75	41	53	Congestion; stomal erosion	Sacrificed, 5 days

Toxin theories relating to infection and septic emboli: Series XI (see Table VIII). In this series of experiments the potential infection or toxemia due to infection was treated and ostensibly prevented by the administration of penicillin-in-beeswax (150,000 units twice daily intramuscularly) in six dogs subjected to 40 per cent burns and daily histamine-in-beeswax injections. Penicillin therapy failed to prevent gastrointestinal pathology in any of the six dogs; definite ulcers were present in five of the six dogs, and bleeding erosions in one. Evidence of bleeding was present in five dogs. All dogs developed increased concentration of the blood, and, when sacrificed (in less than five days), all dogs demonstrated gastrointestinal congestion with gastroduodenal erosions or ulcers.

Fig. 9.—Stomachs and duodenums of dogs subjected to 40 per cent, third degree burns in addition to histamine-in-beeswax administration. Dog 62 (left) was untreated and developed hemoconcentration with mucosal congestion and duodenal erosions in twelve hours, while Dog 65 (right), in which hemoconcentration was prevented, demonstrated no congestion, erosion, or ulcer in three days.

The burned area in these dogs was intact, without gross tissue loss or marked external infection, throughout the one- to three-day duration of this series of experiments, a circumstance not unlike that in burned dogs of other series.

No evidence of septic emboli was noted in the microscopic sections of the ulcers of the stomach and duodenum of nineteen dogs studied.

Products of tissue breakdown as the toxic factor: The blood urea nitrogen as an index of tissue breakdown products or their toxins, determined serially in eighteen burned dogs in the various series of experiments in this study, was elevated for the most part to levels generally consistent with the state of hydration of the animals as shown by blood concentration values.

TABLE VIII. INVESTIGATION OF TOXIN AND INFECTION THEORY

Dogs Subjected to 40 Per Cent Burns and Daily Histamine-in-Beeswax Administration (30 mg. Base) and Treated With Penicillin-in-Beeswax (150,000 Units Intramuscularly Twice Daily)

DOG NUMBER	WEIGHT IN POUNDS	BURN		NUMBER OF HISTAMINE INJECTIONS	NUMBER OF PENICILLIN INJECTIONS	HEMATOCRIT CHANGE		RESULTS	REMARKS
		PER CENT	SECONDS			INITIAL	FINAL		
54	14	40	15	2	5	47	66	Congestion; bleeding antral erosions	Sacrificed, 2 days
55	24	40	15	2	6	43	64	Congestion; pyloric ulcer, two deep bleeding duodenal ulcers	Sacrificed, 2 days
56	28	40	15	2	4	37	47	Congestion; bleeding duodenal ulcer	Sacrificed, 2 days
57	22	40	15	2	5	39	55	Congestion; bleeding pyloric ulcer, antral petechiae	Sacrificed, 2 days
75	30	40	15	1	2	44	56	Congestion; bleeding duodenal ulcer	Sacrificed, 1 day
76	31	40	15	3	6	45	56	Congestion; antral ulcer and petechiae	Sacrificed, 3 days

TABLE IX. INVESTIGATION OF SHOCK FACTOR

Dogs Subjected to 40 Per Cent Burns in Which Serial Blood Pressure Determinations Were Done

DOG NUMBER	WEIGHT IN POUNDS	SYSTOLIC BLOOD PRESSURE		HEMATOCRIT CHANGE		RESULTS	REMARKS
		INITIAL	FINAL	INITIAL	FINAL		
25	22	120	105	42	53	Congestion; pyloric and duodenal ulcers	Died, 3 days, daily histamine injections
31	35	130	95	45	58	Congestion; 2 duodenal ulcers	Sacrificed, 24 hours
35	28	130	120	46	57	Congestion; gastric ulcer and esophageal petechiae	Sacrificed, 4 days after one histamine injection on 3rd day
45	26	125	100	47	56	Congestion; bleeding antral ulcer	Died, 3 days; daily histamine injections
52	31	135	105	40	53	Congestion; large duodenal ulcer; many petechial gastric ulcers	Sacrificed, 24 hours; one histamine injection
56	28	130	100	37	47	Congestion; bleeding duodenal ulcer	Sacrificed, 2 days; penicillin and histamine injections

Shock Factor.—Series XII (see Table IX). Serial blood pressure measurements in six dogs receiving the standard burn (40 per cent, 15 second) in these experiments indicate that alterations of systolic blood pressure do not reach shock level (arbitrarily called 90 mm. of mercury systolic). Therefore, it may be stated that the gastroduodenal pathology (congestion, erosion, or ulcer) is not

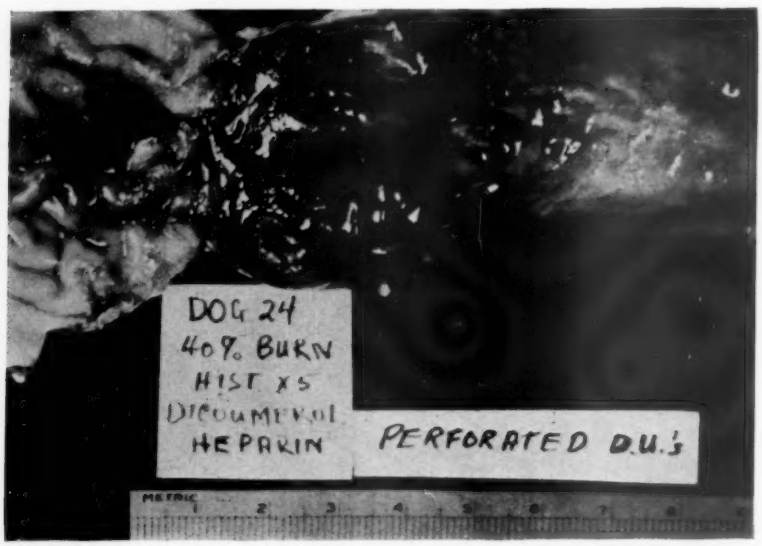

Fig. 10.—Congestion, pyloric and duodenal ulcers in Dog 24 (see Table IV), subjected to 40 per cent, third degree burns and histamine-in-beeswax injections in which the blood was rendered incoagulable by heparin and Dicumarol administration.

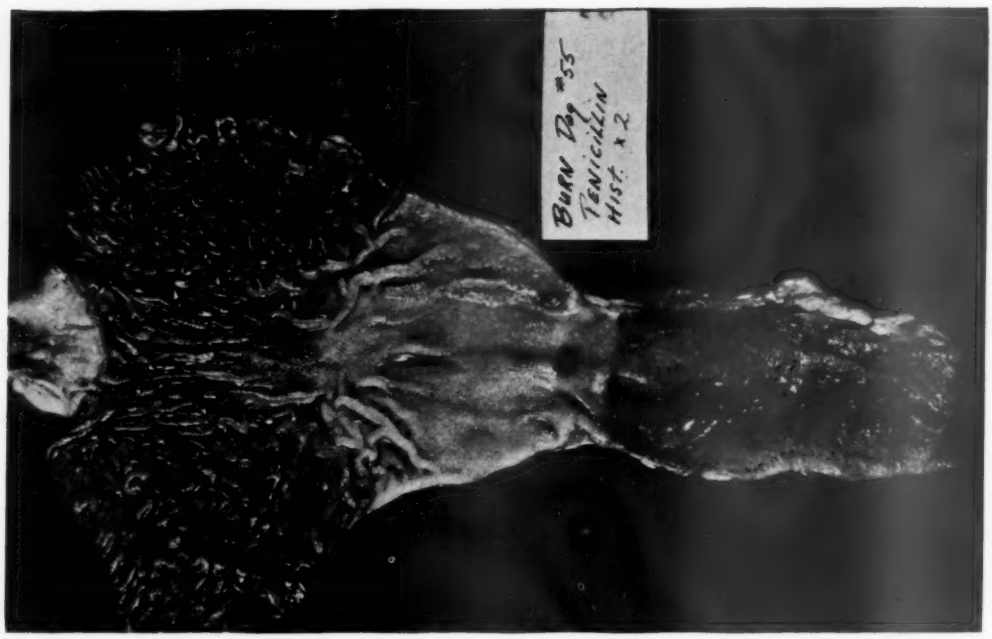

Fig. 11.—Congestion, pyloric and duodenal ulcers in Dog 55 (see Table VIII) in which the potential infection was treated with large doses of penicillin after an extensive burn accompanied by two injections of histamine-in-beeswax mixture. Penicillin therapy failed to prevent the occurrence of ulceration following the burn.

attributable to shock following burns as produced in dogs in the experiments studied. Blood pressure determinations were discontinued when animals were up and walking and "clinically" not in shock.

Adrenal Factor.—Series XIII (see Table X). To test the theory that adrenal insufficiency following burns is the responsible etiological factor in the development of Curling's ulcer, adrenal cortical extract (Cortin 20 dog units per kilogram body weight every twelve hours subcutaneously) was given to four of five dogs subjected to 40 per cent, 15 second burns, and daily histamine-in-beeswax

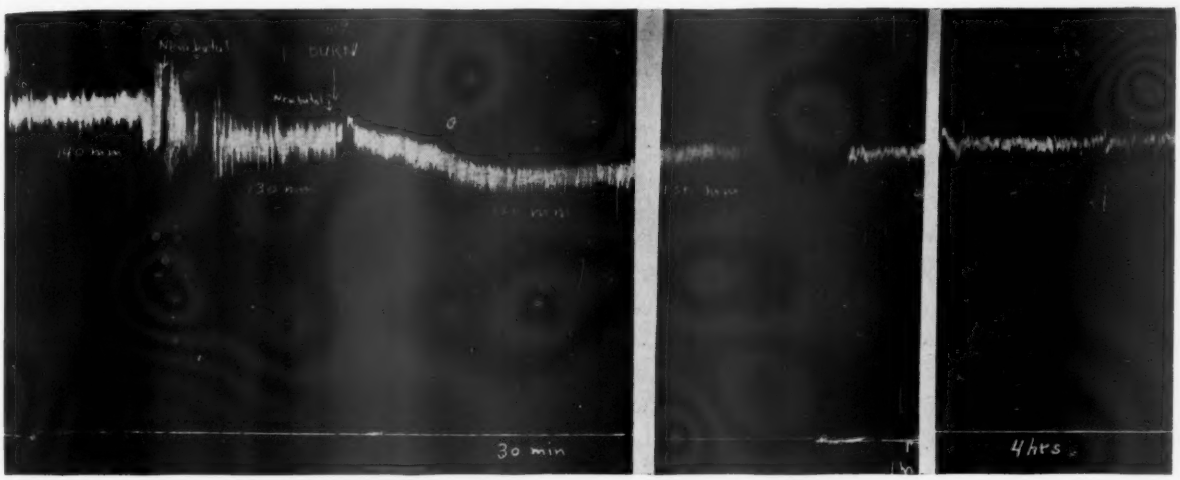

Fig. 12.—Kymographic recording of the systolic blood pressure in a cannulated carotid artery of Dog 35 subjected to a 40 per cent, third degree burn.

Fig. 13.—Congestion and large duodenal ulcers, one perforated into the pancreas in Dog 39 (see Table X) in which massive therapy with adrenal cortical extract was given to prevent adrenal insufficiency following extensive burns. The animal developed hemoconcentration and died on the second day following the burn, after two injections of histamine-in-beeswax mixture.

TABLE X. INVESTIGATION OF THE ADRENAL FACTOR

Dogs Subjected to 40 Per Cent Burns Accompanied by Histamine-in-Beeswax Administration (30 mg. Base); Four of Five Dogs Treated With Subcutaneous Injections of Adrenal Cortical Extract (20 Dog Units Per Kilogram Body Weight Every Twelve Hours)

DOG NUMBER	WEIGHT IN KILOGRAMS	BURN		NUMBER OF HISTAMINE INJECTIONS	DOSE OF CORTIN IN DOG UNITS	HEMATOCRIT CHANGE		BLOOD SUGAR		RESULTS	REMARKS
		PER CENT	SECONDS			INITIAL	FINAL	BEFORE	AFTER		
36	8	40	15	1	0	49	56	91	107	Congestion; small pyloric ulcer; many bleeding points	Sacrificed, 28 hours
37	10	40	15	2	200	43	65	96	100	Congestion; bleeding pyloric ulcers; two large duodenal ulcers	Sacrificed, 48 hours
38	11	40	15	2	200	50	61	81	110	Congestion; bleeding duodenal ulcer; small fundic ulcers	Died in 48 hours
39	10	40	15	2	200	30	41	87	122	Congestion; two large duodenal ulcers, one perforated; fundic ulcers	Died in 48 hours
40	11	40	15	2	220	48	55	82	135	Congestion; three large duodenal ulcers; one large gastric ulcer and other small bleeding pyloric and gastric ulcers	Sacrificed, 48 hours

injections. Massive Cortin therapy to prevent the reported adrenal insufficiency in burned animals failed to prevent the development of gastroduodenal congestion and ulceration in all dogs so treated. All dogs developed increased concentration of the blood following the burn. There was no evidence of adrenal insufficiency in any of the five dogs as measured by blood sugar determinations.

Adrenal glands examined microscopically in twenty-four dogs subjected to burns throughout all experiments showed evidence of hemorrhage in seventeen animals.

DISCUSSION

Of the numerous theories of the etiology and genesis of Curling's ulcer in the literature and noted here, only a small number have been selected for study and subjected to experimental scrutiny. Hence, this research includes those theories and etiological factors which, in the light of present-day concepts of physiology and pathology, appear to have reasonable support and are susceptible to experimental confirmation or rejection.

The dog, the experimental animal in this study, is not subject to spontaneous ulceration of the stomach and duodenum. The occurrence of spontaneous ulcers in normal dogs is practically unknown, a circumstance not existing in other commonly employed animals, and it is in contradistinction to man, in whom spontaneous peptic ulceration is common. The skin of the dog does not "weep" or transude fluid, making it possible to observe the degree of fluid shift to the burned area as a visible edematous swelling, amenable to measurement if desired.

Of all the etiological theories investigated, it is apparent that the occurrence of hemoconcentration is an all-important, if not the sole, factor contributing to the genesis of gastroduodenal ulcer following experimental burns in dogs. The evidence supporting the role of hemoconcentration is repeated directly and indirectly in all series of experiments dealing with the various theoretical factors. Increased concentration of the blood following burns is consistently associated with the development of gastrointestinal congestion, a change from the normal condition of the mucosa which increases the susceptibility of the congested mucosa to injury by the acid-peptic digestive juice. Congestion, with erosion or ulceration, was not seen in a single animal in which hemoconcentration was not present. That hemoconcentration, with its resultant congestion, renders the gastroduodenal mucosa more susceptible to the action of gastric acid-peptic juice is evident in the marked increase in the incidence of ulceration when the administration of histamine-in-beeswax accompanied the burn. Whereas mucosal congestion is the predisposing factor, gastric acidity is undoubtedly the precipitating agent in ulcer formation following burns, which does not necessarily imply that hyperacidity or hypersecretion occurs in burns. It is pertinent here to add that in the experiments in which dogs with gastric pouches were subjected to burns, no increase in gastric acidity or secretion was noted. On the other hand, that the acid factor is important is shown in the decrease in incidence of ulceration in dogs which were subjected to the standard burn and histamine administration, but had reduced gastric acidity by virtue of subtotal gastric resection.

Utilizing the histamine-in-beeswax technique as a maximum stimulus to gastric secretion (ulcer production) provides a useful tool in this investigation

in three ways. The technique necessarily limits the duration of experiments to within five days after the burn, a period of time before some of the devious complications set in; it supplies a measure by which abetting influences favorable to ulcer production may be studied (ulcer within five days favors a predisposing lesion or condition); and finally, it allows evaluation of any particular etiological factor, which, if prevented or altered, may also prevent the development of ulceration even in the face of this maximal stimulant. This latter function is exemplified in a most significant manner in experiments in Series III (Table III), where it is shown that the prevention of the occurrence of hemoconcentration following severe burns portends a normal gastrointestinal tract, even when histamine-in-beeswax is administered daily and the animals are sacrificed in less than five days. This is considered in this work to be prime evidence, along with other data, of the important role of hemoconcentration in the genesis of Curling's ulcer.

Mucosal congestion and ulceration are not specific to the hemoconcentration following burns. This is borne out in the experiments in Series IV and V in which the water compartment (instead of the plasma) of the blood was displaced into a subcutaneous area where hypertonic salt solution had been injected. Findings similar to those observed in burns were noted. A smaller dose of hypertonic solution (10 c.c. per kilogram of 25 per cent sodium chloride) was used in this study to obviate the production of shock for which it was originally described.[28]

Further significant data are presented from the experiments in Series VI to demonstrate the role of hemoconcentration, per se, and not an attending low blood volume or shock, in the development of experimental ulceration. Congestion and ulceration were common findings in dogs with hemoconcentration so produced in less than five days after histamine administration was begun. Histamine administration alone does not produce hemoconcentration or congestion. That shock does not occur in the animals with the standard burn used in this study is shown in Series XII (Table IX).

The effects of hemoconcentration upon vital functions and organic integrity may be directly related to the increased viscosity of the nutrient blood. It has been shown that an increase in the corpuscular volume (red blood cell) from 50 to 70 (measured as hematocrit) doubles the viscosity. Furthermore, the viscosity of the blood is inversely proportional to the rate of flow, the latter being also dependent on the caliber of the capillary or blood vessel. These factors, that is, hemoconcentration, increased viscosity, and decreased blood flow, greatly influence the transport and actual delivery of oxygen to the cell, or influence the organ toward anoxia. Indeed, Underhill and associates[119] have shown that an increase of 40 per cent of normal hematocrit values is incompatible with life.

Thromboembolism.—Many of the effects of hemoconcentration in burns have been attributed to the development of thrombosis or thromboembolic phenomena. The results of the experiments in Series VII (Table IV), in which the blood of burned dogs was rendered incoagulable by prior treatment with heparin and/or Dicumarol, indicate that thrombosis appears to play a very little role, if any, in the development of ulcer-complicating burns. Congestion, erosion, and ulcera-

tion occurred when and if hemoconcentration developed, in a manner similar to its occurrence in dogs which retained an unimpaired clotting mechanism. No evidence of embolic phenomena was found, septic, fatty, or otherwise, even though microscopic studies in a majority of animals, utilizing special techniques, were carried out.

At least four different aspects of theories pertaining to a toxin as the etiological factor in Curling's ulcer were investigated. The transfer-circulation experiments, Series VIII, Table V, are of note in that four donor dogs presented all the evidences predisposing to ulceration when exsanguinated at four, twelve, twenty-four, and forty-eight hours, and yet when this blood, supposedly containing the presumptive burn toxin, was injected into normal dogs almost exsanguinated of their own blood, and the blood of the recipient dogs was then kept at its initial concentration, no evidence of congestion, erosion, or ulcer was demonstrated in five days, in spite of maximal stimulus to ulceration effected by histamine. Cross-circulation experiments would satisfy certain aspects of this particular group of experiments, except that it was thought desirable to control the factor of blood concentration in the recipient animals, a circumstance not attainable in parabiosis experiments.

It is apparent from the results tabulated in Table VIII that penicillin therapy for potential infection or sepsis does not prevent the occurrence of gastroduodenal ulcer following burns as carried out in this study. Again, there was a measurable hemoconcentration in each instance, irrespective of penicillin therapy. The animals in this series of experiments were sacrificed within three days after scalding, the period of time before demonstrable evidence of gross infection is manifest. Cultures of burned tissue or blood, however, were not made.

The results of the experiments of Series XII, Table IX, show that shock, as measured by systolic blood pressure determinations, does not occur following the burns standardized in this study, and therefore is not a significant factor in the etiology of the ulcers demonstrated. Serial systolic blood pressure readings were taken and recorded before and immediately after the burn until the animals were up and walking. It is conceivable that secondary shock may occur as a premortem finding, but it should be noted that a majority of animals were sacrificed before that state developed, and most of them had evidences of a fully developed ulcer (melena, hemetemesis, vomiting, and so on) by twenty-four to forty-eight hours, while still in a reasonable state of well-being and clinically not in shock. It should be repeated here that shock and hemoconcentration are not, in every instance, directly related; one may occur without the other, a circumstance well-demonstrated in this study.

It is shown by the results of experiments in Series XIII, Table X, that the adrenal factor of insufficiency is not important in the etiology of Curling's ulcer. It will be noted that the substitution therapy by adrenal extract for the adrenal insufficiency was massive (some 20 to 40 times more than the amount sufficient to prevent an insufficiency state due to adrenalectomy in dogs). Again, hemoconcentration was present in all dogs in which gastrointestinal pathology was noted. Adrenal insufficiency, by partial or total adrenalectomy, has been shown to favor the development of the histamine-provoked ulcer in dogs.[43]

It should be remembered that in this study the experiments investigated are not designed to indicate the nature of the lethal factor in fatal burns, but only to determine, experimentally, the etiological factor of gastroduodenal ulcer in burns; these factors may be, quite likely, entirely different in their action. A number of animals in these experiments died without developing hemoconcentration. Ulceration from hemoconcentration with its resultant hemorrhage and perforation may, in its own right, occasionally be the cause of death.

The Mechanism of the Development of Curling's Ulcer.—The course of events in the genesis of Curling's ulcer from the inception of the burn to ulceration itself is relatively simple. There is at the time of burn and subsequent to it a transudation of plasma-like fluid through capillaries, in which the permeability has probably been increased by the burn itself, into the tissue at the burned site. This loss of plasma from the vascular space results in increased concentration of the blood which, with its resultant stasis and increased viscosity, produces mucosal congestion (due to general capillary engorgement), extravasation and, occasionally, superficial necrosis. The mucosa, lacking an adequate supply of oxygen, is increasingly susceptible to the erosive action of gastric acid-peptic secretions which are not necessarily increased in degree.

SUMMARY

Investigation into the genesis of gastroduodenal ulcer following burns was carried out in 13 series of experiments utilizing 16 rabbits and 115 dogs, 80 of which were subjected to extensive burns by scalding. The etiological factors subjected to experimental evaluation included hemoconcentration in burns and allied conditions, thromboembolic phenomena (thrombosis and emboli, septic and fatty), toxin (histamine, gastric acidity, infection, sepsis, and products of tissue breakdown), shock, and the adrenal factor.

CONCLUSIONS

Evidence is presented to show that, of the various etiological agents investigated in this study, only the factor of hemoconcentration is important as a predisposing state in the genesis of experimental gastroduodenal ulcer following extensive superficial burns in dogs.

There exists a direct relationship of the occurrence of gastrointestinal congestion to increased concentration of the blood; the former is dependent upon the development of the latter.

Gastroduodenal ulceration occurs only in those animals in which hemoconcentration, with its resultant mucosal congestion, attends the burn, and is not seen when hemoconcentration fails to develop.

Moreover, gastrointestinal abnormality following burns may be prevented by avoidance of the hemoconcentration of burns by proper therapy, even when accompanied by histamine administration.

The incidence of gastroduodenal ulceration provoked by hemoconcentration in burns is markedly increased when histamine-in-beeswax administration accompanies the burn. Conversely, partial ablation of the acid factor experimentally attained by subtotal gastric resection tends to prevent the ulceration but not the mucosal congestion attending severe burns.

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